TWO-WEEK CONTINUOUS MONITORING OF HEART RHYTHM IN CHRONIC KIDNEY DISEASE

by
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Abstract

Individuals with chronic kidney disease (CKD) have an alarmingly high rate of sudden cardiac death, largely attributable to arrhythmias. The burden of arrhythmias has been difficult to study because arrhythmias are often transient and asymptomatic, and the current practice is limited by short periods of arrhythmia monitoring. This dissertation therefore predominantly used a new continuous monitoring device in the Atherosclerosis Risk in Communities study to assess the following four aims.

First, we conducted a systematic review and meta-analysis to examine the burden of all types of arrhythmia in CKD. Most studies found that estimated glomerular filtration rate (eGFR) was associated with a higher risk of atrial fibrillation (AF). Some studies also reported a higher incidence of ventricular arrhythmia related to reduced eGFR, but overall, limited number of studies examined albuminuria and other arrhythmias.

Second, we quantified across CKD severity the burden of major arrhythmias (i.e., AF, non-sustained ventricular tachycardia [NSVT], long pause, atrioventricular block [AVB]) and minor arrhythmias (i.e., ventricular ectopy [VE], supraventricular tachycardia [SVT] and ectopy [SVE]). Compared to no-CKD, CKD was associated with higher presence of AF and NSVT, higher frequency of long pause and VE, and a lower frequency of AVB.

Third, we investigated the relationships between several biomarkers representing cardiac overload (i.e., natriuretic peptide [NT-proBNP]), cardiac injury (i.e., high-

sensitivity cardiac troponin-T [hs-cTnT]), electrolyte abnormalities (i.e., potassium and magnesium), and anemia (i.e., hemoglobin) with arrhythmias in CKD. NT-proBNP and hs-cTnT were associated with many major arrhythmias. Electrolytes were associated with some arrhythmias, while hemoglobin was not robustly associated with any arrhythmias.

Fourth, we characterized the diurnal patterns of intermittent AF and assessed whether they vary by CKD status. There was a biphasic pattern of AF with a peak occurring around midnight and a nadir around noon.

Taken together, this dissertation provided a broader understanding of the burden of various arrhythmias, their risk factors and markers, and a diurnal pattern of AF in CKD. Our research highlights the relevance of various arrhythmias in CKD and the importance of cardiac overload and injury in the pathophysiology of arrhythmias, while demonstrating a diurnal pattern of AF with potential clinical implications.

Dissertation Readers

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I dedicate this dissertation to my parents, Juliet and Paul Kim, and to my grandparents in Korea. Their sacrifice, strength, and love remind me to always dream bigger and that nothing is impossible.

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Introduction

Chronic kidney disease (CKD) is characterized by either or both of a reduced kidney function, as measured by estimated glomerular filtration rate (eGFR), and kidney damage, as typically measured by albuminuria. CKD affects more than 10%-15% of the adult population globally[1] and increases of the risk of cardiovascular disease (CVD). Indeed, CVD is the leading cause of death in individuals with CKD.[2-4]

Sudden cardiac death (SCD), often due to a cardiac arrhythmia, is a major contributor of cardiovascular mortality in CKD.[5] Indeed, end-stage renal disease patients have an overwhelmingly high rate of SCD that accounts for up to 25% of all deaths.[6,7] In earlier stages of CKD, kidney function and albuminuria are also associated with an increased risk of SCD.[8,9] An abnormal myocardium vulnerable to irregular ventricular conduction and electrolyte abnormalities are considered to play an important role in the development of various arrhythmias in CKD,[5,10] but the actual burden and underlying pathogenesis of different arrhythmias in this clinical population are not well-understood. This is a critical knowledge gap to strategize effective and efficient prevention and management of life-threatening arrhythmias in vulnerable population with CKD.

Limited data on arrhythmias across all stages of CKD

Previous studies reporting prevalence estimates of arrhythmias in CKD have been limited to individuals with end-stage renal disease requiring dialysis treatments and/or specific types of arrhythmias. As shown in **Table 1**, there are more studies available

among the dialysis population. However, considering the fact that only approximately 1-1.5% of individuals with CKD are in end-stage,[11] it is important to explore CKD patients who are not receiving dialysis treatments.

In terms of types of arrhythmias, most previous studies explored a single type of arrhythmia, atrial fibrillation (as shown in **Table 1**). This suggests an important relationship between CKD and prevalent atrial fibrillation; however, the burden of other types of arrhythmias, such as ventricular tachycardia or prolonged pauses, remain unclear, especially among those with CKD not requiring dialysis.[12,13]

Even for the relationship between CKD and atrial fibrillation, when we dig the literature deeper, most studies only investigated kidney function but not kidney damage in this context (**Table 2**). This is important to consider because CKD is examined as measure of both kidney function and damage (albuminuria), as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO guidelines) (**Figure 1**). Furthermore, many studies have shown that albuminuria is a potent predictor (often stronger than kidney function) of various cardiovascular phenotypes, therefore, our current understanding of CKD and atrial fibrillation may be underestimated.

The limitations of current heart rhythm monitoring practice

Conventional first-line methods of heart rhythm monitoring such as the clinical 12-lead electrocardiogram (ECG), which records for ~10 seconds, or the ambulatory Holter monitor, which records for 24-48 hours, have a low diagnostic yield, as many

arrhythmias are paroxysmal and asymptomatic, and can take longer time to detect. For asymptomatic arrhythmias, individuals may not even seek an opportunity undergo an ECG test. These arrhythmias are important to diagnose, as asymptomatic or undetected paroxysmal arrhythmias can also lead to adverse events.[14]

A new wearable ECG patch can overcome current limitations

The Zio Patch (iRhythm Technologies Inc., San Francisco, California) allows for up to 14 days of monitoring, which is one of the longest monitoring periods offered by a small non-invasive ECG patch (**Figure 2**). Two weeks of monitoring is suggested to be the optimal duration for monitoring, as a past study on invasive cardiac monitoring has demonstrated that the diagnostic yield of arrhythmias significantly decreases after two weeks (1.04, 0.15, 0.01 additional diagnoses per patient in week 1, 2, 3, respectively).[15] Studies comparing the Zio Patch to the conventional Holter monitor have also shown that the Zio Patch can detect more arrhythmic events (**Table 3**) and is more comfortable and easier to use without the need for removal, thereby allowing a timelier detection of events that could be missed by the Holter monitor.[16]

To date, only a few studies have used the Zio Patch to describe the prevalence of arrhythmias in patients who have clinical indications (e.g., those with history of stroke or transient ischemic attack, those undergoing evaluation or management for atrial fibrillation, etc.) for undergoing Zio Patch monitoring.[16-19] However, data on the presence of different arrhythmias in a community-based setting are sparse. This device will allow

us to compare the burden of various types of arrhythmia in individuals with and without CKD. Moreover, with the continuous ECG monitoring data, we can characterize diurnal patterns of arrhythmias that may be unique to the CKD population and have potential clinical implications.

Importance of identifying risk factors or markers associated with arrhythmias in CKD

Although quantifying disease burden is a critical initial step for strategizing disease prevention and management, kidney function (estimated by eGFR) itself is not currently modifiable, and it is unclear whether circulating biomarkers can help better predict the risk of arrhythmias in CKD. Thus, it is crucial to identify modifiable risk factors or markers of arrhythmias to better manage or risk stratify individuals with CKD at a high risk of arrhythmias. Due to the limited data on the burden of arrhythmias in CKD, the risk factors or markers for various arrhythmias in CKD have not been intensively evaluated. Previous studies identified age, sex, race, smoking, cardiovascular disease, C-reactive protein, and left ventricular hypertrophy as risk factors for prevalent atrial fibrillation in CKD;[20,21] however, the association of cardiac biomarkers, electrolytes, or anemia have not been widely studied in association with various arrhythmias in CKD. We will therefore focus on cardiac biomarkers, electrolyte imbalance, and anemia, as these are common complications in CKD and play important roles in the cardiac action potential as well as cardiac inotropy and chronotropy.

Biologically, serum levels of potassium play critical roles in the electrical conduction of the heart.[22] Magnesium, alongside potassium, has also been implicated in electrophysiological alterations leading to ventricular arrhythmias.[23] Epidemiologic studies have thus demonstrated that these electrolyte levels are associated with cardiovascular mortality and/or SCD; however, their associations with various arrhythmias across stages of CKD are unknown.[22,24-27]

In comparison to electrolytes, the associations of circulating biomarkers such as natriuretic peptide and troponin with various arrhythmias remain relatively unclear, especially by CKD status. Some studies have previously demonstrated a potential link between cardiac biomarkers and atrial fibrillation or ventricular tachycardia;[28-37] however, these studies did not examine the relationships in the context of CKD. Furthermore, the extent to which the cardiac biomarkers may be associated with other types of arrhythmias are unclear according to the literature. It is possible that cardiac biomarkers could be robust markers of various arrhythmias, as levels of natriuretic peptide and troponin could change as a consequence of cardiac stress and damage that could either precede or follow arrhythmias.[28,33,38]

Anemia is implicated in left ventricular remodeling, which can subsequently lead to adverse cardiovascular outcomes; however, the association of anemia with arrhythmia across CKD stages similarly remains unknown.[39]

Characterizing diurnal patterns of atrial fibrillation over two weeks

The importance of chronobiology in cardiovascular-related functions such as blood pressure have been described previously;[40] however, the temporal structure of arrhythmias, especially of atrial fibrillation among CKD given the relatively robust relationship between the two, has not been well-studied[9,41] because most of these studies have looked at the presence or incidence of atrial fibrillation as a dichotomous outcome. To date, very few studies have explored the diurnal patterns of intermittent atrial fibrillation and found inconsistent results, with studies reporting different numbers and timing of peaks and/or nadirs. Also, some studies were limited in terms of data collection by monitoring only for 24 hours or with a transtelephonic ECG relying on patient symptoms or focusing on a specific study population such as those with implantable cardioverter defibrillator.[42-46] Furthermore, some studies investigated only the first episodes of atrial fibrillation, without accounting for repeated episodes and some inadequately treated all episodes within the same individual as independent uncorrelated events. Moreover, none investigated whether diurnal patterns vary by CKD status.

Based on findings from past studies, we propose to characterize diurnal patterns of atrial fibrillation and how these may vary by CKD. Identifying the circadian variation of atrial fibrillation may help uncover underlying biological mechanisms and may have therapeutic implications (e.g., timing of taking antiarrhythmic medication). Furthermore, as arrhythmias are often difficult to detect, identifying 'high-risk' times of onset may help guide future monitoring efforts to maximize the chance of detection. By characterizing

the diurnal patterns of atrial fibrillation, this research will also lay the methodological groundwork for examining the diurnal patterns of other arrhythmias in the future.

Study aims

The objective of the proposed research is to examine the overall burden (presence, frequency, and percent time), risk factors or markers, and diurnal patterns of various arrhythmias in CKD using the Zio Patch in community-dwelling older adults. The specific aims are to:

Aim 1) Conduct a systematic review and meta-analysis to summarize the relationships between CKD and various types of arrhythmia

Aim 2) Examine the two-week summary measures of the burden (presence, frequency, and percent time) of various arrhythmias by CKD status

Aim 3) Identify CKD-related risk factors or markers of various arrhythmias

Aim 4) Characterize the diurnal patterns of atrial fibrillation how the patterns vary by CKD status

Dissertation data source

For Aims 2-4, the analyses were performed using data from the ARIC study. The ARIC study was originally designed to investigate the natural history of atherosclerotic disease from midlife to late-life. It is an ongoing study with participants recruited from

four U.S. communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. Detailed rationale and study design have been described previously.[47] At the baseline study examination (visit 1) during 1987-1989, the study included 15,792 men and women aged 45-64 years, and participants were followed up for six visits (visit 2 in 1990-1992, visit 3 in 1993-1995, visit 4 in 1996-1998, visit 5 in 2011-2013, visit 6 in 2016-2017, visit 7 in 2018-2019). The proposed research used data from study visit 6, when Zio Patch was first applied to ARIC participants.

Generally, study visit clinic examinations included measurements of cardiovascular conditions and risk factors through the following elements: sitting blood pressure; anthropometry; venipuncture (for blood samples to be analyzed); interviews for medical history, and medication use. In addition to clinic examinations, participants were followed up with annual phone interviews, which changed to semi-annual interviews since 2012. The telephone questionnaire included questions on general health, hospitalization, and events such as stroke or transient ischemic attack. The community-wide surveillance component alongside study examinations and semi-annual questionnaires were used to identify medical events including hospitalizations.

Arrhythmias were primarily measured through the Zio Patch. The Zio Patch devices were administered at the ARIC study visit 6 as part of an ancillary study (PI: Dr. Lin Y. Chen). Approximately 4,000 participants who attended visit 6 and did not have a pacemaker or an implantable cardioverter defibrillator (ICD) were asked to wear the Zio Patch, and ~2,600 complied. Each participant wore the device for up to two weeks and

mailed it back to iRhythm (San Francisco, California), where the heart rhythm data were processed using a proprietary algorithm, various arrhythmias were diagnosed, and the results were reviewed by a trained cardiology technician. The Zio Patch diagnosed various major and minor types of arrhythmias as listed in **Table 4**. We had access to two types of data for each arrhythmia: summary-level data (i.e., presence, frequency, percent time) and a more granular dataset consisting of time-specific episodic data (i.e., time of onset and start/end time). For logistical reasons, the time-specific episodic data were only available for atrial fibrillation. The summary-level data was used for Aims 2 and 3, and time-specific episodic data was used to examine diurnal patterns in Aim 4.

Dissertation structure

This dissertation comprises of four chapters that correspond to the four aims and a conclusion. Each chapter is written in manuscript format. The conclusion section summarizes and discusses the overall findings from the dissertation and outlines the steps for future research.

Table 1. Prevalence of various arrhythmias in chronic kidney disease

Arrhythmia types	Chronic kidney disease, non-dialysis			Dialysis		
	# studies	Study population size range	Prevalence range, %	# studies	Study population size range	Prevalence range, %
Atrial/Supraventricular						
Atrial fibrillation	4[20,21,48,49]	900-27,000	3-20	22[41,50-52]	60-200,000	3-27
Premature atrial contractions	0	-	-	2[53,54]	94-221	7-56
Bradycardia	0	-	-	1[13]	66	20
Asystole	0	-	-	1[13]	66	9
Atrioventricular						
Atrioventricular block	0	-	-	1[54]	221	5
Ventricular						
Ventricular fibrillation	0	-	-	2[55,56]	75-110	14-65
Ventricular tachycardia	0	-	-	3[13,55,56]	66-110	2-64
Ventricular arrhythmias, premature contraction	1[57]	111	35	2[53,54]	94-221	12-85[53,54,57]

Table 2. Associations of kidney disease measures with prevalent arrhythmias

Authors (year)	Arrhythmia(s)	Kidney disease measure(s)	Adjusted estimate(s) (95% confidence interval)
Iguchi et al (2008)[58]	AF	eGFR	OR 1.91 (1.54-2.38) for eGFR<63 vs >76 OR 1.12 (0.88-1.42) for eGFR 63-76 vs >76
McManus et al (2009)[48]	AF	eGFR, ACR	OR 3.37 (1.02-11.14) for eGFRcys<62 vs >79 OR 1.59 (0.57-4.40) for eGFRcr<66 vs >85 OR 4.36 (1.45–13.05) for ACR>15 vs <7
Soliman et al (2010)[21]	AF	eGFR	OR 1.12 (0.92-1.35) for eGFR<45 vs ≥45
Ananthapanyasut et al (2010)[49]	AF	eGFR	OR 1.01 (0.99-1.02) per 1 unit of eGFR
Deo et al (2010)[59]	AF	eGFR, cystatin C	OR 1.22 (0.89-1.66) per 1 unit of eGFR OR 1.53 (1.03-2.28) for highest vs lowest quartile of cystatin C
Liu et al (2011)[60]	AF	eGFR, creatinine	OR 1.00 (0.98-1.02) per 1 unit of creatinine OR 0.98 (0.95-1.00) per 1 unit of eGFR
Baber et al (2011)[20]	AF	CKD stages	OR 2.86 (1.38-5.92) for CKD stage 4-5 vs no CKD
Suzuki et al (2012)[61]	AF	eGFR, proteinuria	OR 0.99 (0.98-1.00) per 1 unit of eGFR OR 0.90 (0.55-1.48) for proteinuria vs no proteinuria
Gorczyca-Michta et al (2013)[62]	AF	eGFR	OR 0.99 (0.98-0.99) per 1 unit of GFR
Ohyama et al (2013)[63]	AF	eGFR	OR 2.66 (1.07-6.60) eGFR<60 vs ≥90
Liu et al (2015)[64]	AF	Cystatin C	OR 1.93 (1.12-3.07) per 1 unit of Cystatin C
Ohsawa el at (2016)[65]	AF	ESRD	PR 2.53 (1.88-3.19) for dialysis vs community dwellers
Mene-Afejuku et al (2017)[66]	VT, PVC	Creatinine	OR 0.002 per 1 SD increase in creatinine for PVC OR 4.22 per 1 SD increase in creatinine for VT
Yonezawa et al (2018)[67]	AF	eGFR, creatinine clearance	OR 1.58 (0.86-3.09) for eGFR<60 vs >90

AF=atrial fibrillation; VT=ventricular tachycardia; PVC=premature ventricular contraction; ESRD=end-stage renal disease; OR=odds ratio; SD=standard deviation; eGFR=estimated glomerular filtration rate

Figure 1. Chronic kidney disease (CKD) status and prognosis by glomerular filtration rate (GFR) and albuminuria

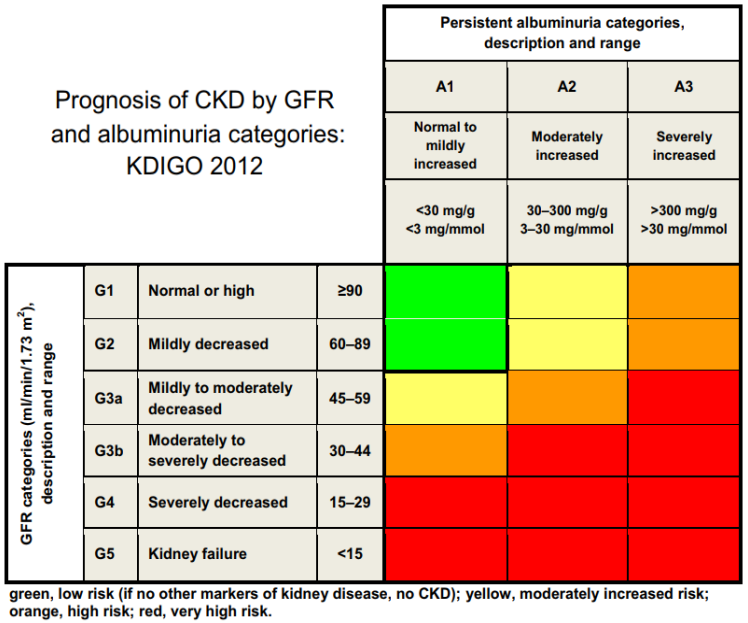


Figure from http://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf

Figure 2. Zio XT Patch (iRhythm Technologies, Inc.)

Table 3. Yield of six types of arrhythmias by 24-hour Holter and Zio XT Patch from study by Barrett et al[16]

		Holter (24 hours) Any of 6 arrhythmias	
		No	At least 1
Zio XT Patch (total wear time) Any of 6 arrhythmias	No	49	1
	Yes	36	60

Six arrhythmias include atrioventricular block, pause, polymorphic ventricular tachycardia, supraventricular tachycardia, ventricular tachycardia, or atrial fibrillation

Table 4. List of arrhythmias and types of data available from the Zio XT Patch

Arrhythmias	Atrial fibrillation/flutter	Ventricular tachycardia /fibrillation	Long pause (>3s)	Atrioventricular block (type 2 and complete)	Ventricular ectopy	Supraventricular tachycardia	Supraventricular ectopy
Presence: occurrence of at least one episode during two weeks (i.e., yes or no for each arrhythmia)	X	X	X	X	X	X	X
Frequency: total count of episodes occurring over two weeks or percent of total analyzable time		X	X	X	X	X	X
Percent time: percentage of device wear time spent in arrhythmia	X						
Time of onset of each arrhythmia episode occurring over two weeks	X						
Start and end time of each episode	X						

Chapter 1. Chronic Kidney Disease and Cardiac Arrhythmias: A Systematic Review and Meta-Analysis

Co-authors: Ning Ding, Junichi Ishigami, Manabu Hishida, Xuejuan Ning, Yijing Feng, Josef Coresh, Lin Y. Chen, Kunihiro Matsushita

Abstract

Rationale & Objective: Chronic kidney disease (CKD) strongly predicts sudden cardiac death and may elevate the risk of certain cardiac arrhythmias like atrial fibrillation (AF); however, the relationships between different measures of CKD and various types of arrhythmia are not well-characterized.

Study design: Systematic review and meta-analysis.

Setting & Study populations: Adults with measures of CKD and arrhythmia.

Selection criteria for studies: Embase and PubMed were searched for prospective, cross-sectional, and case-control studies that were published until July 2018. We performed qualitative assessment of studies using the Newcastle Ottawa Quality Assessment Scale.

Analytical approach: Pooled estimates were obtained using random-effects model.

*Results***:** Among 16,245 articles, we identified 33 prospective (n=24,159,972), 21 cross-sectional (n=253,328), and 4 case-control (n=217,932) studies that included diverse study populations from 19 countries and were mostly high quality. Twenty-four prospective studies examined the relationship between estimated glomerular filtration rate (eGFR) and AF, and demonstrated that lower eGFR was associated with a higher risk of AF

(pooled hazard ratio [HR] for AF 1.72 [95% CI: 1.30, 2.27] comparing reduced vs. referent eGFR groups). A few studies demonstrated that higher albuminuria was associated with AF (pooled HR for AF 2.16 [95% CI: 1.74, 2.67] comparing high vs. low albuminuria). Results were similar for cross-sectional studies. Several prospective studies examined ventricular arrhythmias inducing implantable cardioverter-defibrillator (ICD) shock and reported a higher incidence in the reduced eGFR group (pooled HR for ICD shock 2.32 [95% CI: 1.74, 3.09] comparing reduced vs. referent eGFR groups). Only four studies examined other types of arrhythmia.

Limitations: High heterogeneity across prospective studies and exclusion of non-English articles.

*Conclusion***:** We identified robust data on the CKD-AF relationship. In clinical population requiring ICD, reduced kidney function was associated with life-threatening ventricular arrhythmias. Our review also highlights a large gap in knowledge on other types of arrhythmia in CKD.

Introduction

Chronic kidney disease (CKD) is characterized by reduced kidney function or kidney damage and is a major public health problem that affects over 10% of adults worldwide.[1,68-71] Individuals with CKD, especially at advanced stages, have a high risk of sudden cardiac death (SCD), which suggests that they may also have a high burden of cardiac arrhythmias.[9] Indeed, several studies have demonstrated that there may be a

relationship between CKD and the prevalence or incidence of some types of arrhythmia such as atrial fibrillation and ventricular arrhythmias.[61,72,73] These relationships, however, are not necessarily well-characterized due to the inconsistent definitions for CKD (e.g., estimated glomerular filtration rate [eGFR], albuminuria) across studies.[41] Therefore, it is important to identify all studies examining the associations between different measures of CKD and arrhythmias in order to make appropriate comparisons and conclusions.

Furthermore, it is unknown if and how CKD is associated with arrhythmias other than atrial fibrillation or ventricular arrhythmias such as bradycardias and supraventricular arrhythmias. Recent studies have implicated bradyarrhythmia in addition to ventricular arrhythmia as the terminal arrhythmia leading to SCD in CKD, suggesting that CKD patients may have a high burden of arrhythmias that are not as widely studied.[12,13] Therefore, it is imperative to review the literature and examine the burden of all types of arrhythmia in this high-risk population to provide a better knowledge base of the relationships between CKD and various types of arrhythmia. We therefore conducted a systematic review and meta-analysis of studies reporting relationships between CKD and various types of arrhythmia.

Methods

Literature search strategy

This systematic review was conducted and reported in accordance with the recommendations by the PRISMA guideline.[74] Based on the pre-determined protocols,

we systematically searched prospective, cross-sectional, and case-control studies that examined the association between CKD and arrhythmias in adults aged 18 years or older. We did not impose any restriction on the year of publication. Our search excluded case reports, case series, conference abstracts, narrative reviews, and articles not written in English.

The main exposure of interest was any measure of CKD and included various terms related to kidney disease such as CKD, renal insufficiency, kidney failure, dialysis, uremia, creatinine, cystatin C, eGFR, beta-2-microglobulin, albuminuria, proteinuria, albumin-creatinine ratio (ACR), and urine excretion of albumin or protein. As for the comparison group, since our objective was to examine the association between CKD and cardiac arrhythmia, we were interested in including studies that compared more than one CKD stage (or group or category) so that relative estimates of arrhythmia burden across CKD severity could be provided.

The primary outcome was any type of cardiac arrhythmia that included but was not limited to the following: tachycardia, bradycardia, atrial fibrillation or flutter, atrioventricular block, long pause, premature atrial or ventricular contraction, torsades de pointes, sick sinus syndrome, and other heart rhythm abnormalities.

We performed the literature search on Embase and PubMed for all relevant articles on July 11, 2018 using a detailed search strategy as outlined in **Table A-1**.

Study selection

All articles found through our search strategy were exported to EndNote X7 reference manager (Clarivate Analytics; Thomson Reuters, Philadelphia, PA) by an author (ND) who sorted and removed duplicate articles. The remaining articles were then uploaded to Covidence (Melbourne, Australia), which was the main tool used to screen the articles. Six reviewers (EK, ND, JI, MH, XN, YF) worked in pairs to independently perform title and abstract screening of all articles. All conflicts were resolved by either one of the two reviewers (EK, ND) who did not initially screen the articles involved in the conflict. With the remaining articles, the same six reviewers working in pairs performed full-text screening using the same prespecified inclusion and exclusion criteria while recording reasons for exclusion. Conflicts were resolved by either one of the two reviewers (EK, ND) who did not screen the articles involved in the conflict. We focused on studies that demonstrated associations that adjusted for at least one other variable.

Data collection and quality assessment

Various data elements (as listed in **Table A-2**) were extracted from each article and recorded in Microsoft Excel (Microsoft Office Professional Plus 2016, Microsoft Corporation, Redmond, WA) by six reviewers (EK, ND, JI, MH, XN, YF) who worked in pairs. All conflicts were resolved by discussion between each pair of reviewers.

All studies were assessed for risk of bias and overall quality using variations of the Newcastle Ottawa Quality Assessment Scale (NOS).[75] For prospective studies, we used the NOS for cohort studies (**Table A-3**), which evaluates the quality of studies by

assessing eight items related to selection, comparability, and outcome. The maximum possible score was nine, and a score greater than six was used to indicate a high-quality study. Cross-sectional studies were evaluated using the adapted version of NOS (**Table A-4**) which similarly assessed items related to selection, comparability, and outcome for a maximum possible score of ten.[76] Studies with a score higher than seven were considered high in quality.[77] Case-control studies were evaluated using the NOS for case-control studies (**Table A-5**) that assessed eight items related to selection, comparability, and exposure.[75] The maximum score was nine, and a score higher than six indicated high quality.[78] The quality assessment was performed by pairs of the same six reviewers, and conflicts were resolved by discussion between each pair.

Data synthesis and analysis

We conducted a random-effects meta-analysis to pool the results of prospective studies and cross-sectional studies separately. We chose to categorize studies that examined post-operative arrhythmias among patients who underwent surgery as cross-sectional because even though these studies included some follow-up time, the arrhythmias, mainly atrial fibrillation, were captured during relatively short post-operative periods (typically <30 days). We further separated the analyses by arrhythmia type and different measures of CKD (either eGFR or any measure of albuminuria). We pooled the results only when there were more than two studies that examined the same

arrhythmia type and the same CKD measure. We did not pool results from case-control studies, as there was a limited number of studies.

To examine associations of eGFR with various arrhythmias, we pooled the results that included eGFR calculated based on serum creatinine or cystatin C. When pooling studies that handled eGFR as a categorical variable, we included the hazard ratios (HRs) (for prospective studies) or odds ratios (ORs) (for cross-sectional studies) that compared the reduced eGFR category (defined using the lowest eGFR category available below 60 ml/min/1.73m^2) versus the referent eGFR category (as chosen by the study authors). When pooling studies that included eGFR as a continuous variable, we rescaled the hazard HRs (for prospective studies) or ORs (for cross-sectional studies) so that we could examine the risk or odds of arrhythmias per -15 ml/min/1.73m^2 of eGFR across studies. For studies that examined either ACR or proteinuria, we pooled the HRs or ORs that compared the highest category versus the lowest category. For all analysis, we included estimates from the most extended model (the model with the largest number of covariates) from each study.

We visually checked for potential publication bias using funnel plots. Heterogeneity of studies was assessed using the I^2 statistic, and $I^2 > 75\%$ was used to indicate high heterogeneity. A two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using Stata/SE, version 15 (StataCorp, LLC, College Station, TX).

Results

Search results

We found a total of 16,245 articles from Embase and PubMed. After removing the duplicates (n=69), 16,176 articles underwent title and abstract screening (**Figure 1**). Of those, we excluded 15,977 articles that did not meet our criteria of interest and screened the full texts of the remaining 199 articles. Of the 199 articles, we excluded 141 articles that were available only as abstracts (n=88), only examined unadjusted associations of CKD with arrhythmias (n=17), did not examine arrhythmias (n=13) or kidney disease (n=8), did not include a comparison group (n=9), were reviews (n=5), and were duplicate publications (n=1). After full-text screening, we included 58 articles for qualitative and quantitative analysis (**Figure 1**).

The majority of studies (n=47) examined atrial fibrillation, with its prevalence ranging from 1-59% depending on the study population characteristics, and some (n=7) examined ventricular arrhythmias that were recorded by implantable cardioverter-defibrillators (ICDs). Very few examined other types of arrhythmias such as sick sinus syndrome, bradyarrhythmias, conduction system diseases, and supraventricular tachycardia. Most studies assessed CKD using eGFR, and some used either ACR or proteinuria in addition to eGFR. There were few studies that used serum creatinine or cystatin C without calculating eGFR, and used CKD or end-stage renal disease diagnoses based solely on International Classification of Diseases codes (**Table 1**). The majority of studies were considered high quality (**Table A-6**).

There were 33 prospective studies that altogether consisted of 24,159,972 participants (**Table 2**)[59,72,73,79-108] ; 21 cross-sectional studies consisting of 253,328 participants (**Table A-7**)[20,48,49,58-63,65,67,109-118]; and four case-control studies with a total of 1,694 participants (**Table A-8**).[64,66,119-121] The studies were published between 2003 and 2018 and represented various countries from North America, Asia, and Europe. The study population characteristics were diverse, ranging from population-based cohorts to individuals with ICDs. The mean age of the study participants ranged from 35 to 75 years, and the prevalence of cardiovascular disease and its risk factors varied considerably depending on the study population characteristics (hypertension [range 17-85%], coronary artery disease [2-100%], heart failure [1-100%], and diabetes [3-56%]). Most prospective studies had a mean or median follow-up time of greater than 5 years, and the longest mean follow-up was 17 years.

Atrial Fibrillation

There were 13 studies that examined the association between eGFR as a categorical variable and incident atrial fibrillation (**Table 3, Table A-9, Figure 2**).[59,79,80,84,86,93,99,100,103,107,108] All studies except one reported that the reduced eGFR group (mostly defined as eGFR <30 or <60 ml/min/1.73m^2) had a higher risk of atrial fibrillation compared to the referent eGFR group (mostly defined as eGFR ≥60 or ≥90 ml/min/1.73m^2) in their most extended models, and most associations were statistically significant. The pooled HR was 1.81 (95% CI: 1.43, 2.27; I^2 = 75.1%). Among studies

that examined eGFR as a continuous variable, almost all studies demonstrated that lower eGFR was associated with a higher risk of atrial fibrillation (**Table 4, Table A-10, Figure 3**). The pooled HR for incident atrial fibrillation per -15 ml/min/1.73m^2 in eGFR was 1.05 (95% CI: 1.02, 1.07; I^2 = 80.3%).

Of the 8 studies that examined the cross-sectional association of eGFR categories with atrial fibrillation (**Table A-11, Figure A-1**), all studies reported that the reduced eGFR groups were associated with higher odds of atrial fibrillation compared to the referent eGFR groups, with most associations showing statistical significance. The pooled OR for atrial fibrillation in reduced eGFR vs. referent eGFR was 1.83 (95% CI: 1.49, 2.25; I^2 = 34.1%). Of the 5 studies that examined eGFR as a continuous measure, 4 studies similarly reported higher odds of atrial fibrillation per -15 ml/min/1.73m^2 in eGFR (pooled OR 1.18 [95% CI: 1.01, 1.38], I^2 = 69.3%) (**Table A-12, Figure A-2**).

There were six prospective studies and three cross-sectional studies that examined albuminuria, ACR, or proteinuria, and all but two studies reported that compared to the lowest albuminuria group, the highest albuminuria group was associated with a higher risk or odds of atrial fibrillation (pooled HR 2.16 [95% CI: 1.74, 2.67], I^2 = 74.1%, **Table 5, Table A-13, Figure 4**; pooled OR 2.21 [95% CI: 1.05, 4.68], I^2 = 70.8%, **Table Aa-14, Figure A-3**).

The funnel plots for studies examining the association of eGFR categories with atrial fibrillation did not depict evident publication bias (**Figure A-4**). The funnel plot for

studies examining the association of albuminuria with atrial fibrillation did not indicate signs of publication bias either.

Ventricular Tachycardia or Fibrillation

There were eight prospective studies that examined the incidence of ventricular tachycardia or fibrillation among participants with implanted ICDs. Of these, four studies assessed eGFR in relation to ICD therapy, and reported a 2-fold or 3-fold higher risk of ICD shock among the reduced eGFR group (eGFR <60 ml/min/1.73m^2) compared to the referent eGFR group (eGFR >60 ml/min/1.73m^2). The pooled HR was 2.32 (95% CI: 1.73, 3.09; I^2 = 0%) (**Table 6, Table A-15, Figure 5**). Other prospective studies examined ICD therapy or diagnosed ventricular arrhythmias with various CKD measures such as serum creatinine and diagnosed CKD or ESRD, and found that worse CKD was significantly associated with a higher risk of ventricular arrhythmias (**Table A-16**). One cross-sectional study by Soman et al. showed independent associations of lower creatinine clearance (CrCl) with different types of tachycardia (accelerated idioventricular rhythm, non-sustained and sustained ventricular tachycardia, and ventricular fibrillation) among patients in coronary care unit (**Table A-16**). Two case-control studies by Dalal et al. and Mene-Afejuku et al. similarly reported statistically significant relationships between CKD as measured by eGFR or serum creatinine and ventricular tachycardia or fibrillation (**Table A-16**).

Bradycardia

There were a limited number of studies that examined bradyarrhythmias (two prospective studies, one cross-sectional and one case-control study). Khurshid et al. and Jensen et al. examined the prospective associations of either diagnosed CKD or eGFR with the risk of bradyarrhythmias, conduction system diseases, or sick sinus syndrome after adjusting for various confounders, and found that bradyarrhythmias or conduction system diseases but not sick sinus syndrome were associated with CKD measures.

Soman et al. also examined a few bradyarrhythmias (i.e., complete heart block and asystole) cross-sectionally in relation to CrCl, and found that after adjusting for several important confounders, lower CrCl was associated with higher odds of both arrhythmias (**Table A-16**). In contrast, a case-control study by Lu et al. demonstrated no significant relationship between eGFR and symptomatic bradycardia (**Table A-16**).

Discussion

Our systematic review identified 58 relevant articles examining the associations of CKD measures with various arrhythmias, most of which were prospective and cross-sectional in design. The majority of studies were high quality, published recently, and represented many countries (n=19) from North America, Europe, and Asia. Many studies were relatively large (n>1000) due to the inclusion of several population-based cohorts. Regardless of the study design, the majority of studies examined atrial fibrillation (81% focused on atrial fibrillation vs. 20% on ventricular tachycardia/fibrillation), and regardless of the definition for CKD (mostly based on eGFR, but also included

albuminuria), CKD was consistently associated with a higher risk of atrial fibrillation. There were several prospective studies that also examined life-threatening ventricular arrhythmias that were recorded by ICDs, and all studies demonstrated significant associations between lower kidney function and ICD shock. There were, however, no studies that examined albuminuria in this context. There were only a few prospective, cross-sectional, and case-control studies that examined other types of arrhythmia, and most relationships suggested that CKD was associated with higher risks of various arrhythmias (i.e., ventricular tachycardia and fibrillation, supraventricular arrhythmias, complete heart block, asystole, conduction system diseases); however, some of these studies used only diagnosis-based CKD and CrCl as measures of CKD, and no studies included albuminuria.

The robust association between CKD and atrial fibrillation corroborates and supports conclusions from the Kidney Disease: Improving Global Outcomes (KDIGO) conference which states that there generally seems to be an independent relationship between CKD and the risk of atrial fibrillation.[41] Indeed, most associations between CKD and atrial fibrillation, regardless of the study population characteristics, were consistent and statistically significant.[20,58,61-63,79-81,84,86,87,93,99,100,103,107-109,114] More importantly, our review further demonstrated that regardless of how eGFR is examined (i.e., as a continuous or categorical variable using different cutoffs), lower eGFR is strongly associated with a higher risk of atrial fibrillation, which suggests that this association may consistently exist across the full spectrum of eGFR.[61,80,103,107] We further demonstrated

that in most studies that examined albuminuria, higher albuminuria is generally associated with a higher risk of atrial fibrillation, suggesting that the relationship between CKD and atrial fibrillation is robust.[48,61,63,79,80,86,97,99]

The second most frequently invested arrhythmia in the context of CKD was ventricular arrhythmias.[72,83,105] Of note, compared to the associations for atrial fibrillation, the associations for ICD shock were stronger and more consistent, suggesting that worse kidney function may lead to a higher risk of lethal ventricular arrhythmias than atrial fibrillation. This finding is in line with past studies reporting higher incidence of SCD among CKD.[8,9] The results that we examined, however, were among individuals with ICD; therefore, future studies are needed to further examine the burden of ventricular arrhythmia in CKD patients without ICD. Also, data regarding albuminuria and ventricular arrhythmia are warranted.

Our study identified the limited evidence on the relationships of CKD with other arrhythmia aside from atrial fibrillation and ventricular arrhythmia-related ICD therapy.[66,88,90,117,120,121] While a few studies reported significant associations of low eGFR or high serum creatinine levels with some types of tachycardia and bradycardia,[66,88,90,117,120,121] there still remains a large gap in knowledge about the burden of various arrhythmias across the spectrum of CKD including eGFR and albuminuria stages.

There are several potential mechanisms that may underlie the relationships between CKD measures and the risk of arrhythmias, though they are likely multifactorial.

For example, ischemic heart disease, heart failure, and left ventricular hypertrophy are common in CKD, and resulting cardiac damage and fibrosis may interfere the normal conduction in the heart triggering the development of atrial and ventricular arrhythmia.[4,61,122-126] In addition, chronic pathophysiological conditions in CKD such as neuro-hormonal activations (e.g., renin-angiotensin-aldosterone, sympathetic nervous system), chronic inflammation, and electrolyte abnormality (e.g., high potassium, low magnesium) may also enhance the triggering of arrhythmia.[61,127-131] Finally, multiple comorbidities surrounding CKD such as older age and diabetes may also have some roles. Nonetheless, it remains uncertain the extent to which certain pathophysiology is shared by the different types of arrhythmias.

Our study overall highlights a few potential implications for clinical care and future research. The robust relationship between CKD and atrial fibrillation suggests that healthcare providers should pay attention to atrial fibrillation in patients with CKD. Whether and if so what kind of screening (e.g., 24-holter or longer monitoring using wearable devices[16]) are optimal in this clinical population requires future investigation. This is an important clinical question since the excess risk of stroke in CKD patients has been consistently reported.[132] Similarly, our results suggest that it may be important to monitor and manage severe ventricular arrhythmias among this high-risk population. Since atrial fibrillation and ventricular arrhythmias can be simultaneously monitored, the value of arrhythmia monitoring in CKD should be evaluated comprehensively. The limited data on arrhythmias other than atrial fibrillation and ventricular arrhythmia may

be largely attributed to the shortcoming of conventional heart rhythm monitoring such as routine clinic ECGs and short-term ambulatory devices, which are likely to miss asymptomatic or transient arrhythmia episodes. However, recent advancements in continuous monitoring using non-invasive wearable ECG devices will allow us to investigate a number of arrhythmia types across CKD.

There are a few limitations that should be noted in this study. Likely reflecting a heterogeneity of study designs, populations, and methods, we observed high heterogeneity across prospective studies when examining the relationship between eGFR and atrial fibrillation; therefore, the pooled estimates should be interpreted with caution. Nonetheless, the results were qualitatively consistent (i.e., similar direction of association) in most studies. Our review also excluded articles not written in English and may have excluded some studies from certain geographic regions; however, the articles that we identified were still representative of many countries from various continents.

To our knowledge, this is the first systematic review and meta-analysis summarizing the associations of CKD with various arrhythmias. Our study summarizes that CKD is generally associated with atrial fibrillation and ventricular tachycardia or fibrillation; however, there are limited number of studies that include measures of albuminuria and other types of arrhythmia. Our review supports the importance of monitoring and appropriately managing the high burden of arrhythmias in CKD and highlights critical knowledge gaps to be addressed in future studies.

Figure 1. Flow diagram of study selection

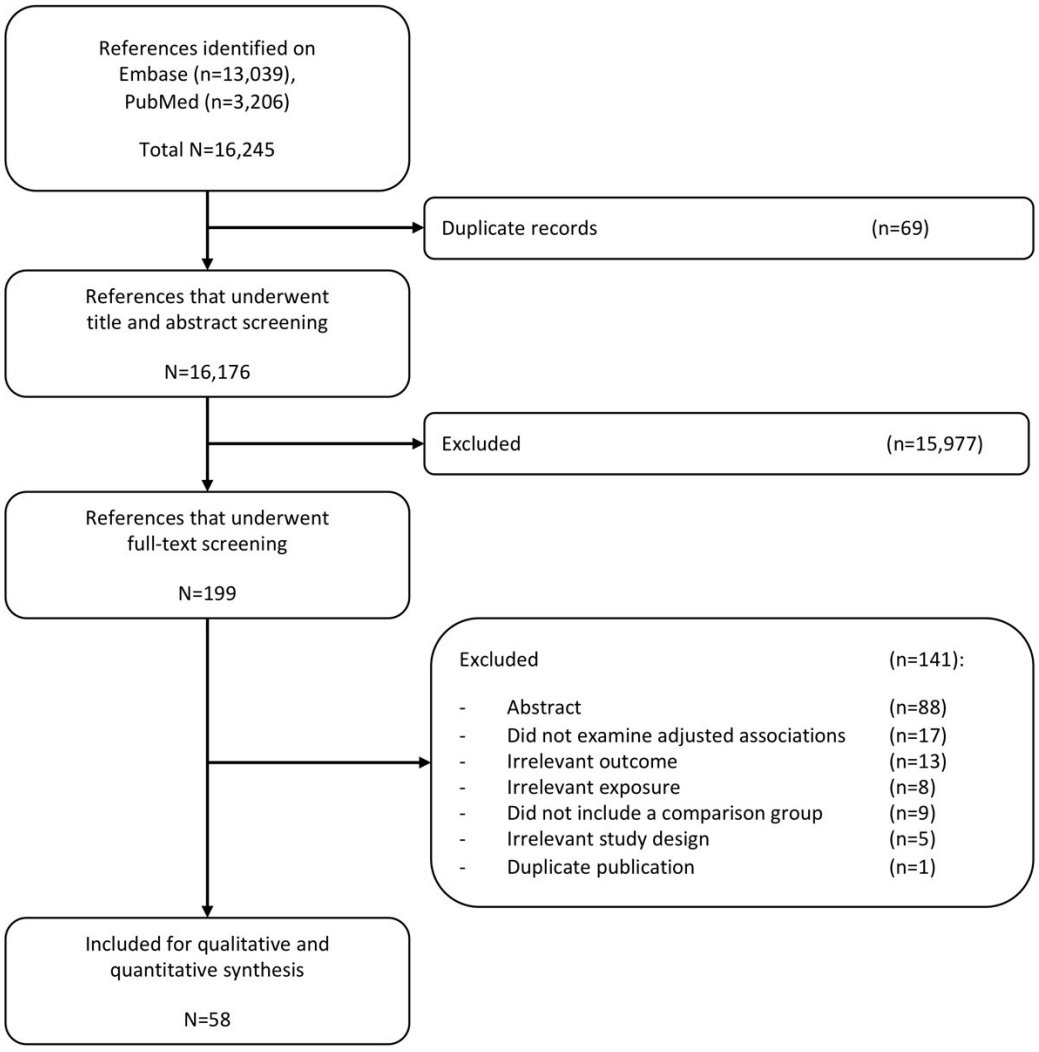


Table 1. Arrhythmia and chronic kidney disease measurements used in the 58 studies included in the systematic review

Prospective studies				
Reference	**Year**	**Arrhythmia type**	**Arrhythmia measurement**	**Chronic kidney disease measurement**
Alonso	2011	AF	Diagnosis codes	eGFR; ACR
Babu	2016	VF/VT	ICD	eGFR
Bansal	2017	AF	ECG, diagnosis codes	eGFR; ACR
Deo[§]	2010	AF	ECG, diagnosis, self-report	eGFR; cystatin C
Eisen	2017	AF	Diagnosis codes	eGFR
Elahi	2003	AF	ECG, notes	Renal failure based on serum creatinine
Hage	2011	ICD therapy	ICD	eGFR
Hai	2017	Sudden arrhythmic death or sustained VT requiring ICD therapy	Death, ICD	eGFR
Horio	2010	AF	ECG	eGFR and proteinuria combined
Hreybe	2006	ICD shock for VF or VT	ICD	Serum creatinine
Hsu	2013	AF and flutter	Diagnosis codes	eGFR; proteinuria
Iguchi	2010	AF	ECG	eGFR
Jensen	2013	AF	ECG, diagnosis codes	Cystatin C
Jensen	2014	Sick sinus syndrome	Diagnosis codes	eGFR; cystatin C
Khurshid	2018	AF or flutter, bradyarrhythmias, conduction system diseases, supra-ventricular arrhythmias, or ventricular arrhythmias	Diagnosis codes	CKD based on diagnosis codes
Kreuz	2010	ICD therapy for malignant ventricular arrhythmias	ICD	Serum creatinine
Kreuz	2011	ICD therapy for malignant ventricular arrhythmias	ICD	Serum creatinine
Laukkanen	2016	AF	Linkage to registry	eGFR
Lee	2016	AF	Diagnosis codes	ESRD based on diagnosis codes

Liao	2017	AF	Diagnosis codes	ESRD based on diagnosis codes
Liao	2015	AF	Diagnosis codes	ESRD based on diagnosis codes
Lim	2017	AF	Diagnosis codes	Proteinuria
Marcos	2017	AF	ECG	eGFR; cystatin C; serum creatinine; urine albumin; ACR; urine albumin excretion
Molnar	2017	AF	Diagnosis codes	eGFR; ACR
Naruse	2011	AF recurrence	ECG	eGFR
Nelson	2012	AF	Diagnosis codes	CKD based on diagnosis codes
Robin	2006	ICD shock for VF	ICD	ESRD
Sciacqua	2014	AF	ECG, diagnosis codes, other documents	eGFR; CKD
Shen	2016	AF	Diagnosis codes	ESRD
Takahashi	2009	ICD shock for VF	ICD	eGFR
Tokuda	2011	AF recurrence	ECG	eGFR
Watanabe	2009	AF	ECG	eGFR
Xu	2015	AF	ECG	eGFR
Cross-sectional studies				
Reference	**Year**	**Arrhythmia type**	**Arrhythmia measurement**	**Chronic kidney disease measurement**
Ananthapanyasut	2010	AF	ECG, medical record	eGFR
Auer	2007	AF	ECG, notes	eGFR
Baber	2011	AF	ECG	eGFR and ACR combined
Chua	2013	AF	ECG	eGFR
Deo[§]	2010	AF	ECG, diagnosis, self-report	eGFR; cystatin C
Deshmukh	2017	AF	ECG, implantable device, telemetry	Serum creatinine
Gorczyca-Michta	2013	AF	Medical records	eGFR
Hashemzadeh	2013	AF	ECG	Renal dysfunction based on creatinine*
Iguchi	2008	AF	ECG	eGFR
Karatas	2015	AF	ECG	Serum creatinine
Limite	2016	AF	ECG	eGFR
Liu	2011	AF	ECG, medical record	eGFR; serum creatinine
McManus	2009	AF	ECG	eGFR; ACR
Nisanoglu	2007	AF	ECG	Renal dysfunction based on serum creatinine
Ohsawa	2016	AF	ECG	Dialysis
Ohyama	2013	AF	ECG	eGFR; proteinuria
Soliman	2010	AF	ECG, self-report	eGFR

Soman	2002	AF or flutter, VT, VF, complete heart block, asystole	Charts	CrCl; dialysis
Suzuki	2012	AF (paroxysmal, persistent)	ECG	eGFR; proteinuria
Todorov	2017	AF (new onset, permanent)	Patient files	Serum creatinine
Yonezawa	2018	AF	ECG	eGFR; creatinine clearance
Case-control studies				
Reference	**Year**	**Arrhythmia type**	**Arrhythmia measurement**	**Chronic kidney disease measurement**
Dalal	2012	VF	ECG	eGFR
Liu	2015	AF	ECG, medical history, physical exam	Cystatin C
Lu	2016	Symptomatic bradycardia	ECG	eGFR
Mene-Afejuku	2017	PVC, VT	ECG	Serum creatinine

CKD=chronic kidney disease; AF=atrial fibrillation; VT=ventricular tachycardia; VF=ventricular fibrillation; PVC=premature ventricular contraction; ICD=implantable cardioverter defibrillator; eGFR=estimated glomerular filtration rate; ACR=albumin-creatinine ratio; ESRD=end-stage renal disease

[§] This study is listed as both prospective and cross-sectional because it includes examinations of incident and prevalent atrial fibrillation

* Unable to identify if creatinine is serum or urine creatinine

Table 2. Summary of 34 prospective studies included in the systematic review

Study	Year	Region	N	Population characteristic	Age (mean [SD])	Male, %	Hypertension, %	Current smoking, %	SBP (mean [SD])	CAD, %	HF, %	Stroke, %	Diabetes, %	Follow-up
Prospective studies														
Alonso	2011	USA	10,328	Population-based	62.7 (5.7)	43.2	45.9	14.8	-	7.6	5.8	-	15.9	Median 10.1 years
Babu	2016	United Kingdom	199	Single center-based patients with CRT-D therapy	66.1 (12.1)	72.9	-	-	-	-	-	-	-	Mean 55.5 (30) months &
Bansal	2017	USA	16,769	Population-based	63.1 (12.0)	41.6	-	12.8	129.8 (20.8)		3.4	2.5	16.2	Mean 8.5 (2.7) years§
Deo§	2010	USA	4,663	Population-based outpatients	75.3 (5.3)	41.7	41.6	9.7	-	21.6	6.0	-	15.5	Mean 7.4 years
Eisen	2017	Israel	2,605,271	Health system-based	48.4 (16.2)**	42.6**	27.2**	7.4**	-	-	-	-	9.9**	Mean 8.7 years
Elahi	2003	United Kingdom	877	Single center-based patients who underwent CABG surgery	63.9 (8.7)	78.9	58.2	6.1	-	100	-	-	19.7	1 year
Hage	2011	USA	696	Single center-based patients with ICD implantation	58.7 (14.9)	71.4	-	-	-	33.8	81.3	12.6	31.5	Mean 2.1 (1) year
Hai	2017	China	918	Single center-based inpatients with acute coronary syndrome	65.3 (13.3)	75.6	55.1	25.3	-	21.2	-	-	33.9	Mean 1.4 years
Horio	2010	Japan	1,118	Single center-based outpatients without previous heart disease	63.0 (11.0)	52.0	-	48.0	146.0 (16.0)	-	-	-	24.0	Mean 4.5 years
Hreybe	2006	USA	230	Single center-based patients with ICD implantation	62.7 (13.8)	78.7	-	17.0	-	75.2	100	-	31.7	Mean 489 (280) days

Hsu	2013	USA	30,533	Population-based outpatients with HIV	47.1 (10.9)	97.2	17.2	9.4	-	1.6	0.9	0.4	3.7	Median 6.8 years
Iguchi	2010	Japan	30,010	Population-based	73.0 (66.0-78.0)*	32.9	46.8	7.1	132.0 (120.0-144)*	-	-	-	-	1 year
Jensen	2013	USA	5,685	Population-based	72.7 (5.7)	42.0	65.2	-	136.3 (21.5)	-	-	-	15.9	Mean 11.2 years
Jensen	2014	USA	20,572	Community-based cohort	58.9 (10.1)	43.5	40.9		125.4 (20.7)	8.3	4.5	2.4	12.9	Mean 17 years
Khurshid	2018	United Kingdom	502,627	Population-based	58.0 (50.0-63.0)*	45.6	28.4	11.2	-	3.1	0.6	1.6	5.5	Median 7 years
Kreuz	2010	Germany	94	Single center-based patients with ICD implantation	66.5 (11.5)	-	54.3	-	-	80.9	-	-	17.0	Mean 34 (20) months
Kreuz	2011	Germany	99	Single center-based patients with ICD implantation	64.1 (14.3)	69.7	26.3	-	-	10.1	-	-	16.2	Median 89 months
Laukkanen	2016	Finland	1,840	Population-based	71.1 (5.8)	66.9	-	-	135.0 (17.9)	29.3	9.8	-	13.3	Median 3.7 years
Lee	2016	South Korea	40,500	Population-based	61.7 (11.0)	53.2	58.1	-	-	3.8	5.0	8.1	-	Mean 5.9 (0.6) years
Liao	2015	Taiwan	404,703	Population-based CKD/ESRD patients and controls	61.7 (14.3)	49.5	84.6	-	-	16.7	34.0	27.1	56.4	Mean 5.1 years
Liao	2017	Taiwan	18,617	Population-based cohort with and without COPD	62.0 (11.5)	75.4	29.9	-	-	-	1.98	7.71	7.8	15 years
Lim	2017	Korea	18,201,275	Population-based	45.3 (14.6)	53.3	28.7	26.0	123.4 (16.6)	2.5	0.6	1.0	9.0	Mean 9.6 years
Marcos	2017	Netherlands	8,265	Cohort study participants	49.0 (13.0)	49.8	27.8	44.7	129.0 (20.0)	3.1	0.2	0.7	3.8	Mean 9.8 (2.3) years
Molnar	2017	Canada	736,666	Population-based	59.8 (12.2)	50.4	59.0	-	-	15.3	4.4	1.0	42.4	Median 6 years
Naruse	2011	Japan	221	Single center-based patients who underwent catheter ablation	59.0 (11.0)	81.0	58.0	-	-	-	-	-	9.0	Mean 31.9 (7.6) months

Nelson	2012	USA	1,092,649	Medicare-based	70.0-74.0***	40.8	54.9	-	-	19.6	6.7	7.3	20.4	Median 24 months
Robin	2006	USA	585	Single center-based patients with ICD implantation	63.0 (15.0)	79.0	51.0	-	-	51.0	-	-	17.0	Mean 2.2 years
Sciacqua	2014	Italy	3,549	Population-based	60.7 (10.6)	52.4	67.9	39.4	142.1 (18.1)	-	-	-	16.4	Mean 53.3 months
Shen	2016	Taiwan	63,788	Population-based patients receiving renal replacement therapy	60.8 (13.6)	47.8	41.3	-	-	16.1	9.0	-	23.4	Mean 8-10 years
Takahashi	2009	Japan	274	Single center-based patients who received ICD implantation	54.0 (16.0)	71.0	-	-	-	-	-	-	-	Median 27 months
Tokuda	2011	Japan	224	Single center-based patients who underwent catheter ablation	55.3 (11.7)	83.5	25.0	-	-	-	13.8	-	-	Mean 37.4 (24.4) months
Watanabe	2009	Japan	223,877	Population-based	60.9 (11.7)	32.0	-	-	129.8 (17.8)	-	-	-	6.0	Mean 5.9 years
Xu	2015	Japan	132,250	Population-based	59.3 (9.3)	31.5	-	27.6	133.5 (17.4)	-	-	-	2.5	Mean 13.8 years

* Median with interquartile interval
** Characteristics of only those without cardiovascular disease
*** Age range for 25% of the study population
^ Percentage of participants with LVEF <30%
[&] Among the control group
[$] In the JHS study only
[§] This study is listed as both prospective and cross-sectional because it includes examinations of incident and prevalent atrial fibrillation

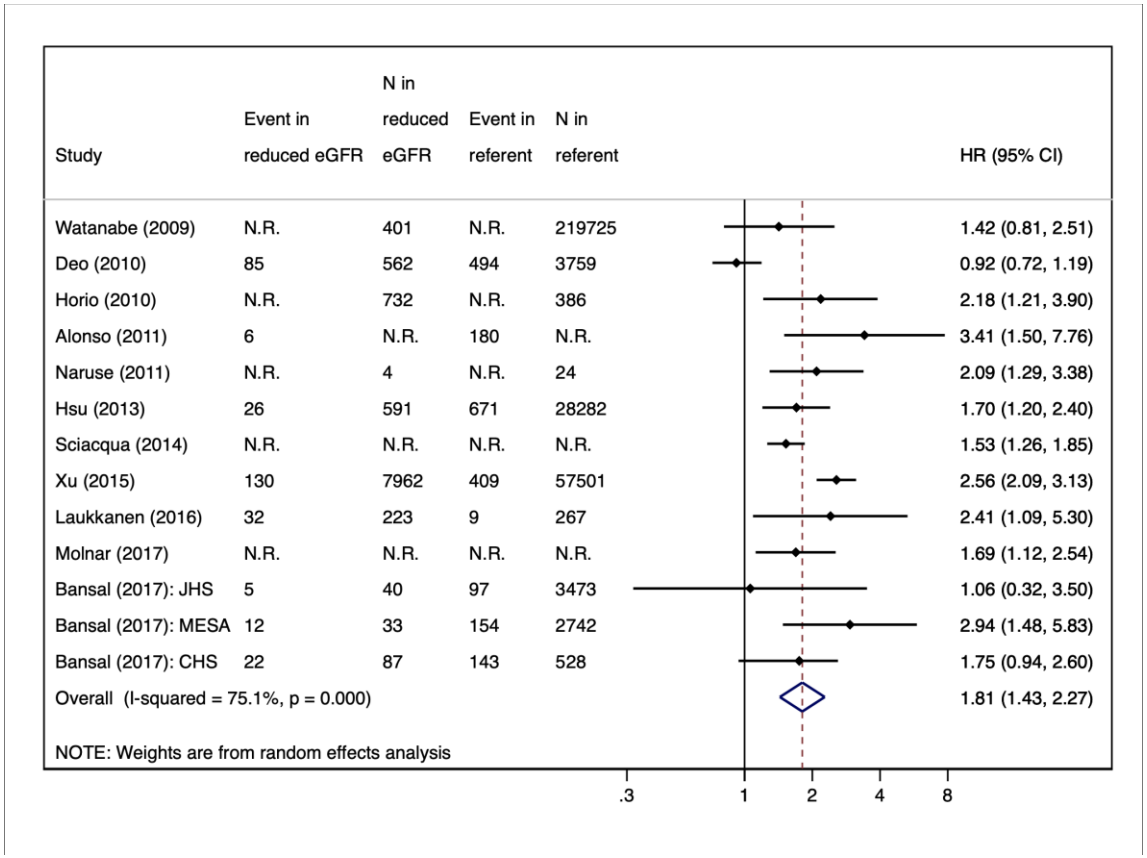
Table 3. Summary of prospective study results on the association between eGFR groups and atrial fibrillation

Study	Year	eGFR categories (ml/min/ 1.73m^2)	Referent group (ml/mi/1. 73m^2)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted covariates**							
						Age	Sex	Race	Blood pressure	Diabetes	Smoking	Lipids	Other
Watanabe	2010	≥60, 30-59, <30	≥60	Not reported	30-59: 1.29 (1.05-1.58), <30: 1.42 (0.81-2.51)	✓	✓		✓	✓			✓
Deo	2010	≥60, <60	≥60	1.29 (1.02-1.64)	0.92 (0.72-1.19)	✓	✓		✓	✓		✓	✓
Horio	2010	≥60, <60	≥60	2.99 (1.77-5.05)	2.18 (1.21-3.90)	✓					✓		✓
Alonso	2011	≥90, 60-89, 30-59, 15-29	≥90	Not reported	60-89: 0.91 (0.76-1.09), 30-59: 1.24 (0.97-1.57), 15-29: 3.41 (1.50-7.76)	✓	✓	✓	✓	✓	✓		✓
Naruse	2011	≥60, <60	≥60	2.035 (1.311-3.159)	2.089 (1.292–3.378)	✓	✓						✓
Hsu	2013	≥60, 30-59, <30	≥60	Not reported	30-59: 1.1 (0.8-1.4), <30: 1.7 (1.2-2.4)	✓	✓	✓		✓	✓		✓
Sciacqua	2014	>60, ≤60	>60	Not reported	1.528 (1.261-1.851)	✓	✓			✓	✓	✓	✓
Xu	2015	≥90, 60-90, <60	≥90	Not reported	60-90: 1.38 (1.21-1.56), <60: 2.56 (2.09-3.13)	✓	✓		✓	✓	✓	✓	✓
Laukkanen	2016	≥90, 60-89, 15-59	≥90	Not reported	60-89: 1.44 (0.99-2.11), 15-59: 2.74 (1.56-4.81)	✓	✓		✓	✓			✓
Molnar	2017	>90, 60-90, 45-60, 30-45, 15-30, <15*	>90	Not reported	60-90: 1.09 (1.06-1.13), 45-60: 1.27 (1.21-1.32), 30-45: 1.43 (1.36-1.51), 15-30: 1.55 (1.41-1.69), <15: 1.69 (1.12-2.54)	✓	✓			✓			✓
Bansal: JHS	2017	≥90, 60-89, 45-59,	≥90	Not reported	60-89: 1.32 (0.98, 1.76), 45-59: 0.97 (0.51, 1.83), 30-44: 1.86 (0.84, 4.13),	✓	✓		✓	✓	✓		✓

		30-44, <30			<30: 1.06 (0.32, 3.50)								
Bansal: MESA	2017	≥90, 60-89, 45-59, 30-44, <30	≥90	Not reported	60-89: 1.09 (0.89, 1.34), 45-59: 1.33 (1.00, 1.77), 30-44: 1.62 (1.05, 2.51), <30: 2.94 (1.48, 5.83)	✓	✓		✓	✓	✓		✓
Bansal: CHS	2017	≥90, 60-89, 45-59, 30-44, <30	≥90	Not reported	60-89: 1.03 (0.86, 1.24), 45-59: 1.12 (0.91, 1.38), 30-44: 1.48 (1.12, 1.94), <30: 1.57 (0.94, 2.60)	✓	✓		✓	✓	✓		✓

eGFR is calculated using serum creatinine
* indicates eGFR calculated among those with albumin-creatinine ratio <3
** full list of covariates available in **Table A-9**

Figure 2. Hazard ratios (HRs) of atrial fibrillation comparing reduced to referent eGFR groups from prospective studies



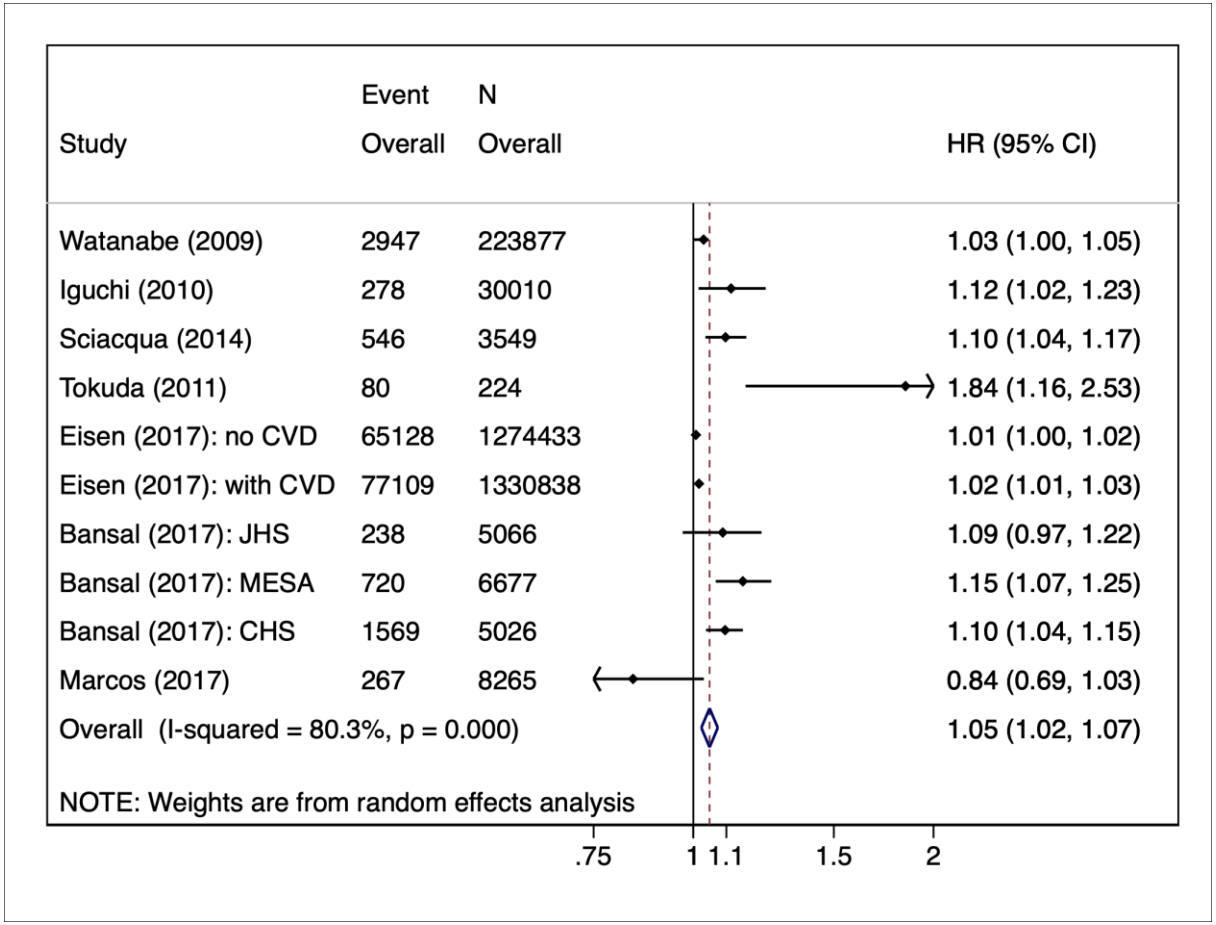
The diamonds and their widths represent HRs and 95% confidence intervals, respectively. The cutoff values for reduced and referent eGFR groups are (in ml/min/1.73m^2): Watanabe (2009) <30 vs. ≥60, Deo (2010) <60 vs. ≥60, Horio (2010) <60 and proteinuria 1+ vs. ≥60, Alonso (2011) 15-29 vs. ≥90, Naruse (2011) <60 vs. ≥60, Hsu (2013) <30 vs. ≥60, Sciacqua (2014) ≤60 vs. >60, Xu (2015) <60 vs. ≥90, Laukkanen (2016) 15-59 vs. ≥90, Molnar (2017) <15 and ACR <3 vs. >90 and ACR <3, Bansal (2017) <30 vs. ≥90.

Table 4. Summary of prospective study results on the association between continuous eGFR and atrial fibrillation

Study	Year	eGFR scale (ml/min/1.73m^2)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted covariates*							
					Age	Sex	Race	Blood pressure	Diabetes	Smoking	Lipids	Other
Watanabe	2009	Per -10	Not reported	1.02 (1.00-1.03)	✓	✓		✓	✓			✓
Iguchi	2010	Per 10	Not reported	0.93 (0.87-0.99)	✓	✓			✓		✓	✓
Tokuda	2011	Per 1	Not reported	0.96 (0.94, 0.99)								✓
Sciacqua	2014	Per 10	0.94 (0.903-0.977)	0.94 (0.903-0.977)	✓	✓		✓		✓	✓	✓
Eisen: No CVD	2017	Per -10	Not reported	1.005 (0.998-1.011)	✓	✓			✓			✓
Eisen: With CVD	2017	Per -10	Not reported	1.011 (1.005-1.018)	✓	✓			✓			✓
Bansal: JHS	2017	Per -20	Not reported	1.12 (0.96, 1.30)	✓	✓		✓	✓	✓		✓
Bansal: MESA	2017	Per -20	Not reported	1.21 (1.09, 1.35)	✓	✓		✓	✓	✓		✓
Bansal: CHS	2017	Per -20	Not reported	1.13 (1.05, 1.21)	✓	✓		✓	✓	✓		✓
Macros	2017	Per 15	0.73 (0.62–0.86)	1.19 (0.97–1.45)	✓	✓			✓	✓		✓

* Full list of covariates listed in **Table A-10**

Figure 3. Hazard ratios (HRs) of atrial fibrillation per -15 ml/min/1.73m^2 of eGFR from prospective studies



The diamonds and their widths represent HRs and 95% confidence intervals, respectively. HRs are rescaled for all studies.

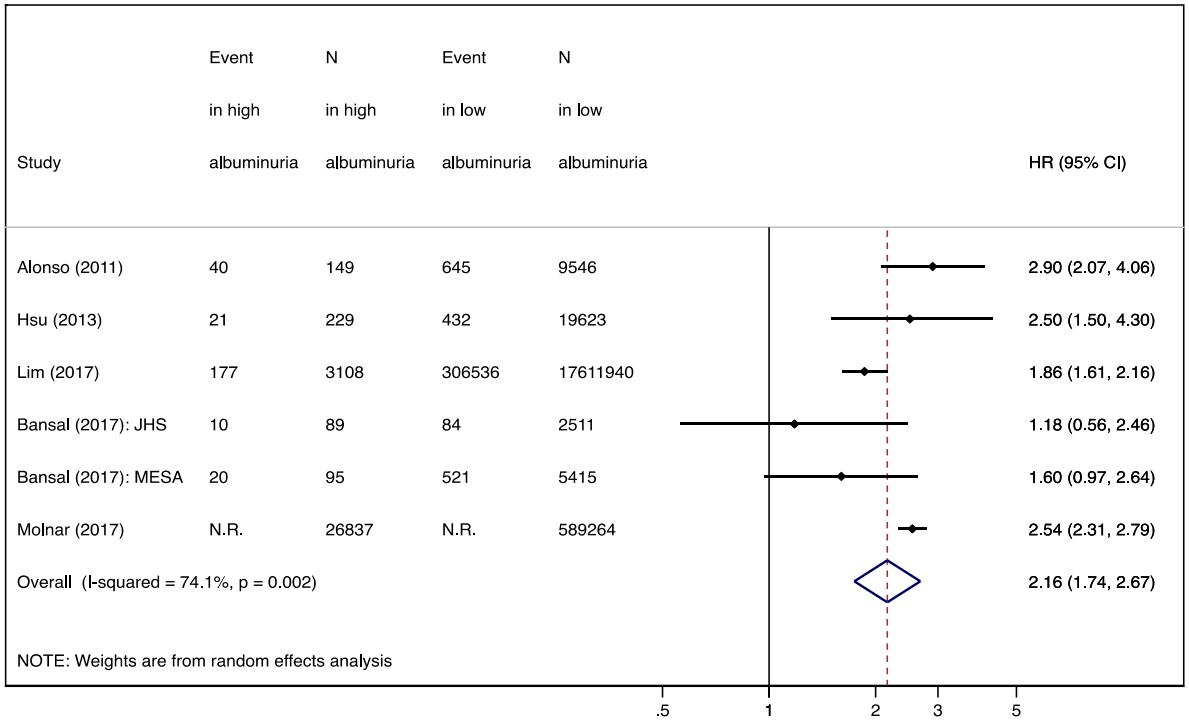
Table 5. Summary of prospective study results on the association between albuminuria groups and atrial fibrillation

Study	Year	Albuminuria categories	Referent group	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted covariates**							
						Age	Sex	Race	Blood pressure	Diabetes	Smoking	Lipids	Other
Alonso	2011	ACR (mg/g): <30, 30-299, ≥300	<30	Not reported	30-299: 1.91 (1.53-2.39), ≥300: 2.90 (2.07-4.06)	✓	✓	✓	✓	✓	✓		✓
Hsu	2013	Proteinuria (mg/dl): 0, 30, 100, 300, ≥2000	0	Not reported	30: 1.5 (1.2-1.8), 100: 1.4 (1.0-2.0), 300: 1.7 (1.1-2.5), ≥2000: 2.5 (1.5-4.3)	✓	✓	✓		✓			✓
Lim	2017	Dipstick protein: Negative, Trace, 1+, 2+, 3+, 4+	Negative	Not reported	Trace: 1.13 (1.10-1.16), 1+: 1.34 (1.31-1.38), 2+: 1.53 (1.48-1.58), 3+: 1.82 (1.71-1.94), 4+: 1.86 (1.61-2.16)	✓	✓			✓	✓	✓	✓
Bansal: JHS	2017	ACR (mg/g): <15 15-29, 30-299, ≥300	<15	Not reported	15-29: 1.21 (0.76, 1.95), 30-299: 1.16 (0.74, 1.82), ≥300: 1.18 (0.56, 2.46)	✓	✓		✓	✓	✓		✓
Bansal: MESA	2017	ACR (mg/g): <15 15-29, 30-299, ≥300	<15	Not reported	15-29: 0.91 (0.71, 1.18), 30-299: 1.44 (1.15, 1.82), ≥300: 1.60 (0.97, 2.64)	✓	✓		✓	✓	✓		✓
Molnar	2017	ACR (mg/g): <3, 3-30, >30*	<3	Not reported	3-30: 1.52 (1.45-1.6), >30: 2.54 (2.31-2.79)	✓	✓			✓			✓

* Among those with eGFR >90

** Full list of covariates in **Table A-13**

Figure 4. Hazard ratios (HRs) of atrial fibrillation comparing high to low albuminuria groups from prospective studies



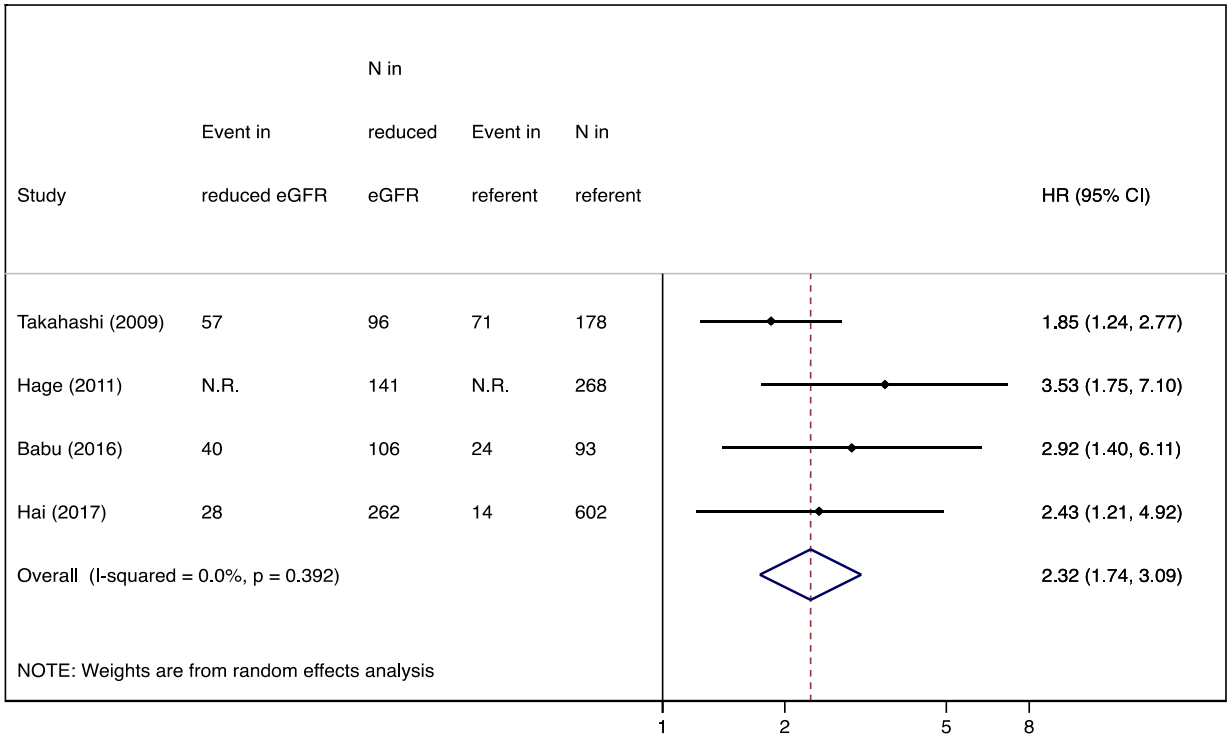
The diamonds and their widths represent HRs and 95% confidence intervals, respectively. The cutoff values for high and low albuminuria groups are: Alonso (2011): ACR ≥300 vs. <30 mg/g; Hsu (2013): Proteinuria ≥2000 vs 0 mg/dl; Lim (2017) Dipstick 4+ vs. negative; Bansal-JHS (2017): ACR ≥300 vs. <15 mg/g; Bansal-MESA (2017) ACR ≥300 vs. <15 mg/g;
Molnar (2017) ACR >30 vs. <3 mg/g.

Table 6. Summary of prospective study results on the association between eGFR groups and ICD shock

Study	Year	eGFR categories (ml/min/ 1.73m^2)	Referent group (ml/min/ 1.73m^2)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted covariates*							
						Age	Sex	Race	Blood pressure	Diabetes	Smoking	Lipids	Other
Takahashi	2009	≥60, <60	≥60	1.81 (1.23-2.66)	1.85 (1.24-2.77)								✓
Hage	2011	≥60, <60	≥60	Not reported	3.53 (1.75-7.10)	✓	✓						✓
Babu	2016	>60, ≤60	>60	2.034 (1.219-3.394)	2.924 (1.399-6.109)	✓	✓						✓
Hai	2017	>60, <60	>60	5.43 (2.86-10.33)	2.43 (1.21-4.92)	✓							✓

* Full list of covariates in **Table A-15**

Figure 5. Hazard ratios (HRs) of ICD shock comparing reduced to referent eGFR groups from prospective studies



The diamonds and their widths represent HRs and 95% confidence intervals, respectively. The cutoff values (in ml/min/1.73m^2) for reduced and referent eGFR groups are: Takahashi (2009) <60 vs. ≥60, Hage (2011) <60 vs. ≥60, Babu (2016) ≤60 vs. >60, Hai (2017) <60 vs. ≥60.

Chapter 2. Two-week burden of arrhythmias across chronic kidney disease severity in a large community-based cohort: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background: Chronic kidney disease (CKD) is associated with sudden cardiac death and atrial fibrillation (AF). However, other types of arrhythmias and different burden measures (e.g., presence and frequency) have not been well-characterized in CKD. We therefore comprehensively quantified the burden of arrhythmias across CKD severity in community-dwelling older adults.

Methods: In 2257 ARIC participants aged 71-94 years who underwent 2 weeks of non-invasive single-lead electrocardiogram monitoring using the Zio XT Patch, we examined the associations of major arrhythmias (AF, non-sustained ventricular tachycardia [NSVT], long pause [>3 sec], Mobitz II or complete atrioventricular block [AVB]) and minor arrhythmias (ventricular ectopy [VE], and supraventricular tachycardia [SVT] and ectopy [SVE]) with CKD severity categorized as no CKD (low risk) and CKD with moderate, high, and very high risk according to estimated glomerular filtration rate (eGFR) and albuminuria. We examined various types of arrhythmia burden: presence, frequency, and percent time in arrhythmia.

Results: CKD with very high risk (vs. no CKD) had a higher prevalence of AF (12.8% vs. 5.0%), NSVT (37.4% vs. 25.8%), long pause (5.8% vs. 1.7%), and VE (99.2% vs. 98.6%). After adjusting for potential confounders, CKD with higher risk remained significantly associated with the presence of AF and NSVT. When we examined other burden measures, CKD severity was significantly associated with a higher percent of time in AF, higher frequency of long pause and VE episodes, and a lower frequency of AVB. When eGFR and albuminuria were examined separately, albuminuria was more strongly associated with arrhythmias.

Conclusions: CKD is associated with the presence of AF and NSVT. Additionally, CKD is related to percent time of AF and higher frequency of long pause and VE. Using a novel 2-week monitoring approach, this study found a broader range of arrhythmias associated with CKD than previously reported.

Introduction

Chronic kidney disease (CKD) is associated with an increased risk of sudden cardiac death (SCD),[9] implying a high burden of cardiac arrhythmias in CKD. Previous studies, however, have focused mainly on atrial fibrillation (AF) or studied patients on dialysis,[59,65,79,95,98,99,104,133] which mainly reflects the difficulty in detecting arrhythmias that can often be asymptomatic and transient. Recent findings demonstrating that bradyarrhythmia can lead to SCD[13,134] and that the vast majority of persons with CKD are

not on dialysis[135] highlight our incomplete understanding of the range of tachy- and bradyarrhythmias that are associated with CKD.

Recent advancements in wearable continuous electrocardiogram (ECG) devices that can monitor for a longer time allow us to investigate other arrhythmias that are asymptomatic and transient in populations other than dialysis patient samples. In addition, they can provide information on different measures of arrhythmic burden, such as the frequency of episodes and percent time in arrhythmias. We therefore used data from a two-week continuous ECG monitoring device in the Atherosclerosis Risk in Communities (ARIC) study to comprehensively examine various arrhythmias (e.g., AF, ventricular tachycardia, long pause, atrioventricular block) and different burden measures (i.e., prevalence, frequency, and percent time) across CKD severity. We hypothesized that more severe CKD is associated with a broader range of arrhythmias, especially when burden measures beyond mere presence or absence of arrhythmias are investigated.

Methods

Study design

This study is a cross-sectional analysis using data from visit 6 (2016-2017) of the ARIC study, which was originally designed to investigate the natural history of atherosclerotic disease from mid- to late-life.[47] The ARIC study design has been published previously.[47] Briefly, 15,792 participants were recruited during 1987-1989 from four communities in the U.S. (Forsyth County, NC, Jackson, MS, Minneapolis, MN,

and Washington County, MD) and completed the first study visit (visit 1). The participants subsequently completed six study visits (visit 2 in 1990-1992; visit 3 in 1993-1995; visit 4 in 1996-1998; visit 5 in 2011-2013; visit 6 in 2016-2017; and visit 7 in 2018-19). Additionally, they were contacted annually (semi-annually beginning in 2012) to obtain updated information on medical history and lifestyle. In visit 6, 4,003 participants attended the study examination which included assessment for cardiovascular disease, cognitive function, and their risk factors, biospecimen collection, medication assessment, and a two-week continuous ECG monitoring. The ARIC study was approved by the institutional review board of each participating center, and written informed consent was obtained from participants at each study visit.

Study population

Of 4,003 visit 6 participants, those who did not have a pacemaker or an implantable cardioverter defibrillator were asked to undergo a two-week ECG monitoring, as detailed below. We excluded participants who did not undergo the continuous ECG monitoring (n=1,387), were missing CKD measures (n=194), and were non-white and non-black (n=6). We also excluded those who were missing any covariate of interest (n=147) (**Figure B-1**). The final analytical sample of this study was 2,257.

Kidney disease measures

The primary exposure of interest was CKD status, which was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) staging criteria for CKD

based on the comprehensive risk of adverse clinical outcomes: no CKD (low risk group), CKD with moderate risk, CKD with high risk, and CKD with very high risk.[136] The groups were categorized based on a combination of values of estimated glomerular filtration rate (eGFR), which indicates kidney function, and albuminuria, which reflects kidney damage (**Figure B-2**). We also secondarily examined eGFR and albuminuria separately. eGFR was calculated based on the CKD-EPI equation using cystatin C,[137] which was measured in serum using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (Roche Diagnostics, Indianapolis, IN) with a laboratory inter-assay CV of 6.1% at a mean concentration of 0.94 mg/L. We used cystatin C rather than serum creatinine, as there is concern that age-related reduced muscle mass can overestimate eGFR in older individuals when using a creatinine-based equation.[138] Albuminuria was measured using albumin-to-creatinine ratio (ACR), which was calculated by dividing urine albumin by urine creatinine as recommended by the KDIGO clinical practice guideline for CKD.[139] Urine albumin was measured in urine on the ProSpec nephelometric analyzer using an immunoturbidometric method (Dade Behring GMBH. Marburg, Germany) with a laboratory inter-assay CV of 4.0% at a mean concentration of 19.7 mg/L. Urine creatinine was measured on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a creatinase enzymatic method (Roche Diagnostics, Indianapolis, IN) that yielded a CV of 4.5% at a mean concentration of 17 mg/dL.

Arrhythmia measurement

The Zio XT Patch (iRhythm Technologies Inc., San Francisco, CA) is a Food and Drug Administration (FDA)-approved ECG skin patch that is single-lead, non-invasive, lightweight, and water-resistant monitor that allows ECG recording for up to 14 days.[16] Compared to the standard 24-hour Holter monitor, the Zio Patch is demonstrated to detect more arrhythmic events and shown to be more comfortable to wear.[16] ARIC study participants were asked to wear the Zio Patch for up to 14 days and mail the device back to the manufacturer, where the ECG data were analyzed using a FDA-approved proprietary algorithm and underwent technical review. The following arrhythmias were detected by the Zio Patch and were included in this study: *major types* including AF, non-sustained ventricular tachycardia, long pause lasting >3 seconds, and Mobitz type II or third-degree atrioventricular block; and *minor types* including ventricular ectopy, supraventricular tachycardia (not including AF), and supraventricular ectopy.

As a result of continuous monitoring, we were able to examine different measures of arrhythmic burden. We first assessed the presence of arrhythmias, dichotomous information of the occurrence of any arrhythmic episode during the monitoring period, and this was measured for all types of arrhythmias. We also assessed the frequency of arrhythmia during the monitoring period, which was defined as the number of episodes per day, and this was measured for all types of arrhythmias except for AF. For AF, instead, we examined the percent time in arrhythmia because the frequency of episodes

will not appropriately reflect the burden of longer lasting AF (e.g., the frequency equals one in the case of continuous AF).

Covariate measurements

All variables were assessed at ARIC study visit 6, except for education, which was measured at visit 1. Educational background was categorized as less than high school, graduated from high school or vocational school, or obtained college or graduate/professional degrees. Body mass index was calculated by dividing body mass (kg) by height squared (m^2). Cigarette smoking and alcohol drinking was self-reported and categorized as current or noncurrent. Diabetes was defined as fasting plasma glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, using medication for diabetes, or self-reported physician diagnosis of diabetes. Total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using an enzymatic method and the Olympus HDL-Cholesterol test, respectively.[140] Prevalent cardiovascular disease included coronary heart disease, heart failure, and stroke, which included self-reported prevalence and visit 1 and relevant events between visit 1 and visit 6 adjudicated by physician reviewers based on medical records from hospitalization data. Systolic and diastolic blood pressure were measured in a sitting position after five minutes of rest using a validated automatic sphygmomanometer (OMRON HEM-907 XL). The average of the last two of three measures was used. Use of antihypertensive medication in the past 4 weeks was assessed by self-report and confirmed with drug containers if available. Similarly, the use of

antiarrhythmic medications was recorded by inspecting the participants' drug containers for all classes of antiarrhythmic medications. For certain types of antiarrhythmic medications that may have overlapping indications (i.e., beta-blockers may be used for some arrhythmias or hypertension), we used self-reported data to confirm if individuals have hypertension and classified the medications as antihypertensive drugs accordingly. We also identified medications that are commonly reported to be QT-prolonging (**Table B-1**),[141] as QT prolongation can affect the risk of arrhythmias.[142]

Statistical analysis

We examined the distributions of all variables and summarized them using mean and standard deviation (SD) for normally distributed continuous variables; median and interquartile interval (IQI) for non-normally distributed variables; and frequency and percentage for categorical variables.

The associations between CKD status and the presence of each arrhythmia were estimated using Poisson regression with robust variance to accommodate the high prevalence of some arrhythmias.[143] The group with no CKD served as the reference group. The same method was used to examine eGFR and ACR separately.

The relationships between CKD measures and the frequency of arrhythmia episodes were estimated using a zero-inflated Poisson regression with robust variance to account for an excess of zero counts, taking into consideration the total analyzable wear time of the device as the offset variable to explore frequency as the rate of arrhythmias

across CKD status. The zero-inflation portion of the model included the same set of covariates as the Poisson model. The associations between CKD measures and percent time in AF were examined using linear regression.

For all associations, we adjusted for potential confounders in a series of models: model 1 was unadjusted; model 2 adjusted for age, sex, race, study center, and education; model 3 additionally included body mass index, current smoking, alcohol use, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total cholesterol, HDL cholesterol, antiarrhythmic and QT-prolonging medications. In analyses that examined eGFR or ACR as the main exposure, we additionally adjusted for ACR or eGFR, respectively, in model 3. When examining minor arrhythmias originating from the supraventricular region (i.e., supraventricular tachycardia and supraventricular ectopy), we excluded participants who had continuous AF since continuous AF would likely preclude participants from experiencing these supraventricular arrhythmias.

To test the robustness of our findings, we performed the following sensitivity analyses. We ascertained additional prevalent cases of the major types of arrhythmias (AF, non-sustained ventricular tachycardia, long pause, and atrioventricular block) using hospitalization records collected within 1 year of visit 6. We chose a time frame of 1 year to capture current cases and avoid additionally including older events that may have been treated and no longer relevant. Using the additional prevalent events of arrhythmias, we re-examined the associations between CKD status and the presence of arrhythmias. As antiarrhythmic medications can potentially affect the risk of various arrhythmias, we also

performed the main set of analyses after excluding participants using antiarrhythmic medications.

All analyses were performed in R 3.5.1 and Stata/SE 15.1 (StataCorp, College Station, TX). A two-tailed P <0.05 was considered statistically significant.

Results

Baseline characteristics

Of 2,257 participants, 58% had CKD (30% with moderate risk, 17% with high risk, and 11% with very high risk). Compared to participants without CKD, individuals with CKD were older, less educated, and less likely to drink alcohol; had higher body mass index and systolic blood pressure; were more likely to take antihypertensive medication and have diabetes and prevalent cardiovascular disease; and had slightly lower total cholesterol and HDL cholesterol (**Table 1**). The majority of participants wore the Zio Patch for the full two weeks. The device wear-time was comparable across CKD status, with a median wear-time of 13.7 days (IQI 12.7, 13.9) in the total study population.

Descriptive statistics of arrhythmias across CKD

Those who had CKD with moderate to very high risk had a higher two-week prevalence of major arrhythmias (i.e., AF, ventricular tachycardia, long pause, and atrioventricular block) compared to participants without CKD (39.1% in CKD vs. 28.5% in no CKD). In particular, CKD with very high risk showed the highest prevalence of AF

(12.8% vs. 5.0% in no CKD), non-sustained ventricular tachycardia (37.4% vs. 25.8%), and long pause (5.8% vs. 1.7%) (**Table 2**). The two-week prevalence of supraventricular tachycardia was slightly lower among those with CKD compared to those without.

In addition to the presence of arrhythmias, those with CKD also had a higher percent time in AF and had more frequent episodes of ventricular ectopy and supraventricular ectopy (**Table 2**).

Prevalence ratio for major arrhythmias across CKD

In unadjusted models, CKD with moderate to very high risk demonstrated significant prevalence ratios for AF, non-sustained ventricular tachycardia, and long pause compared to no CKD (Model 1 in **Figure 1** and **Table B-2**). In this model, a dose-response relationship was generally observed for AF, ventricular tachycardia, and long pause. The adjustment for demographic factors only slightly attenuated these associations (Model 2 in **Figure 1** and **Table B-2**). Additionally adjusting for clinical risk factors, cardiovascular disease, and medications (Model 3 in **Figure 1** and **Table B-2**), the prevalence ratios remained statistically significant for AF in CKD with very high risk (prevalence ratio [PR] 1.91 [95% CI: 1.21, 3.01]) and for non-sustained ventricular tachycardia in CKD with high risk (PR 1.20 [95% CI: 1.01, 1.44]). In contrast, the results for atrioventricular block were quite different, with either similar or lower prevalence ratios in those with CKD compared to no CKD (bottom of **Figure 1**).

When eGFR and ACR were examined separately, lower eGFR was associated with a higher prevalence of AF, non-sustained ventricular tachycardia, and long pause in crude (Model 1) and demographically-adjusted (Model 2) models (**Figure B-3, Table B-3**); however, after adjusting for other potential confounders and ACR (Model 3), these associations were no longer significant. On the other hand, the associations of ACR with AF and non-sustained ventricular tachycardia were robust across all models (PR 1.27 [1.13, 1.44] for AF and 1.07 [1.01, 1.13] for ventricular tachycardia in Model 3). Its association with long pause was statistically significant only in Model 1. Neither eGFR nor ACR was significantly associated with atrioventricular block, although both lower eGFR and higher ACR demonstrated inverse associations in Models 3.

Percent time in atrial fibrillation and frequency of other major arrhythmias

Compared to no CKD, CKD with moderate to very high risk had an increasingly higher percent time in AF, and the associations involving CKD with high and very high risk remained statistically significant throughout all models (**Figure 2A**, **Table B-4**).

When examining the frequency of arrhythmia episodes, we found that CKD with moderate to very high risk had a higher frequency of long pause even after adjusting for potential confounders (Rate ratio [RR] 17.73 [95% CI: 3.91, 80.37]) compared to the no CKD group (**Figure 2B, Table B-4**). Conversely, CKD status was consistently associated with a lower frequency of atrioventricular block in all models. There were no significant

associations between CKD status and the frequency of non-sustained ventricular tachycardia.[144]

Both eGFR and ACR were generally associated with percent time in AF but only the association for ACR remained statistically significant in all four models (**Figure B-4A, Table B-5**). Lower eGFR and higher ACR demonstrated similar associations with a higher frequency of long pause (**Figure B-4B, Table B-5**). Neither of eGFR or ACR showed significant associations with frequency of ventricular tachycardia. As for the frequency of atrioventricular block, both lower eGFR and higher ACR demonstrated inverse relationships in Model 1, but the relationship was robust only for eGFR across the three models.

Prevalence and frequency of minor arrhythmias across CKD

CKD with high risk and very high risk were associated a higher prevalence of ventricular ectopy in crude (Model 1) and demographically-adjusted (Model 2) models but not in Model 3 (**Figure B-5, Table B-6**). When we examined the frequency of ventricular ectopy, however, CKD with very high risk consistently demonstrated a significantly higher rate ratio in all models (**Figure B-6, Table B-7**). There were no clear robust patterns with respect to the prevalence or frequency of supraventricular tachycardia and supraventricular ectopy.

Lower eGFR and higher ACR were similarly associated with the prevalence of ventricular ectopy (**Figure B-7, Table B-8**) while only ACR was significantly associated

with a higher frequency of ventricular ectopy in all models (**Figure B-8, Table B-9**). Neither eGFR nor ACR was significantly associated with the prevalence or frequency of supraventricular tachycardia. For supraventricular ectopy, eGFR and ACR similarly demonstrated significant associations with its prevalence in Models 1 or 2 but not with its frequency.

Sensitivity analysis

Using hospitalization records, we ascertained 26 additional prevalent cases of AF, 1 additional ventricular tachycardia, 3 additional long pause, and 3 additional atrioventricular block events. When we used the additional events to re-examine the relationship between CKD status and the prevalence of the major arrhythmias, the findings remained similar: CKD with higher risk groups were associated with a higher prevalence of AF and ventricular tachycardia (**Table B-10**). When we excluded participants taking antiarrhythmic medications, the results were also similar but the association between CKD status and ventricular tachycardia was attenuated (**Table B-11**).

Discussion

In this community-based study with excellent adherence to a two-week continuous ECG monitor, we found a higher prevalence of clinically significant arrhythmias such as AF and non-sustained ventricular tachycardia among those with more severe CKD, indicating a dose-response relationship across the spectrum of CKD

severity. Of the major types of arrhythmias, AF demonstrated the most consistent association with CKD severity, regardless of the type of burden examined (i.e., the prevalence and percent time in arrhythmia). While the presence of other major arrhythmias such as long pause and atrioventricular block were not associated with CKD, when we further examined other types of arrhythmic burden, we found that CKD with higher risk was associated with higher frequency of long pause and with lower frequency of atrioventricular block. Similarly, we observed a robust association between CKD with very high risk and higher frequency of ventricular ectopy. When we examined eGFR and ACR separately, we found that ACR was associated with more arrhythmias overall.

Despite several published studies suggesting that CKD is associated with a higher burden of AF,[20,21,48,59] there still remains an important knowledge gap on the prevalence and burden of AF across the severity of CKD.[41] In past studies, the prevalence of AF ranged from <1% to >49% in CKD,[20,21,49,59,61,67,110] which is a fairly large range that can be attributed to different study populations (e.g., inpatients, population-based cohorts, patients receiving dialysis, etc.), different definitions of CKD (e.g., eGFR calculated using various formulae and filtration markers, proteinuria, dialysis status, etc.), and different methods used to record arrhythmias (e.g., Holter monitors, clinic or study visit ECGs, self-report, etc.). In our study of community-dwelling older adults using continuous ECG monitoring and a definition of CKD that includes both eGFR and ACR, we report a two-week prevalence of AF ranging from 5% to 13% depending on CKD severity, which remained similar even after using hospitalization records to ascertain

additional prevalent cases. The independent association between CKD and the prevalence of AF in the present study was consistent with previous studies.[20,48,59] Moreover, we uniquely observed that CKD severity was also strongly associated with higher percent time of AF, further supporting the close link between CKD and AF.

We also found that CKD status was associated with a higher prevalence of non-sustained ventricular tachycardia, which corroborates past studies reporting that individuals with CKD have a higher risk of incident life-threatening ventricular arrhythmias as captured by implantable cardioverter defibrillators (ICDs).[9,120] We also found that the frequency of ventricular ectopy (though not the binary presence of ventricular ectopy) was higher among those with more severe CKD, which has not been widely reported in the past. Taken together, our findings suggest that CKD is associated with a higher risk of ventricular arrhythmias of varying severity (ectopic beats to non-sustained tachycardia), which can explain high burden of SCD among CKD;[8,9] however, further studies are needed to more clearly examine the relationship between various ventricular arrhythmias and SCD.

In addition to AF and ventricular arrhythmias, quantifying the burden of other arrhythmias is especially important as more recent studies have implicated the role of bradyarrhythmia in SCD among CKD.[13,134] In this context, we observed the higher frequency of long pause in CKD vs. no CKD. To our knowledge, this is the first report of this relationship in a community-based cohort, although it is in line with recent small studies ($n < 70$) reporting bradycardia as an important terminal arrhythmia leading to

SCD in patients on dialysis.[13,134] While further research is warranted to better understand the relationship between long pause and SCD in CKD, our results further support the need to pay attention to bradycardia in clinical practice and research in CKD patients.

We unexpectedly observed that those with more severe CKD had a lower frequency of atrioventricular block. The pathophysiology underlying this association is unclear, and we are not aware of any previous reports showing this association. It is possible that less frequent episodes of heart block among those with more severe CKD might indicate longer durations of block; however, we cannot test this theory since the Zio Patch did not report durations of AV block. Thus, this observation needs to be confirmed in other studies, and if so, the clinical impact of AV block as detected by the Zio Patch should be also evaluated.

When we compared eGFR and ACR separately, ACR was more strongly associated with the presence of major arrhythmias. While only a few studies have examined both eGFR and albuminuria with prevalent AF,[48,61,63] one study similarly demonstrated that urinary ACR was more strongly associated with the presence of AF compared to eGFR.[48] The present study extended our knowledge to ventricular tachycardia and other arrhythmias. The precise mechanism underlying the associations of ACR with arrhythmias is unknown; however, ACR is also considered a marker of microvascular damage, a pathophysiological condition known to play an important role in cardiac dysfunction. Indeed, ACR has been shown to strongly predict incident heart

failure.[3] Thus, it is possible that ACR could broadly reflect subclinical cardiac abnormalities that increase vulnerability to major arrhythmias.

In light of our findings, our study overall demonstrates the importance of examining different types of arrhythmia burden, as this provided additional insights into the relationships between CKD and various arrhythmias that would have been missed by relying only on the presence vs. absence of arrhythmias. Further, it highlights the value of continuous monitoring devices and supports recent statements from the American Heart Association emphasizing the importance of moving beyond examining arrhythmias only as a binary entity.[145] Although the prognostic value of our findings cannot be investigated at this moment, the ARIC Study is an ongoing prospective study and thus will be able to eventually address this important question.

There are several limitations of our study to be discussed. Although better detection than 24 hour Holter,[16] 2-week monitoring with the Zio Patch may still have missed some prevalent cases. Indeed, additional yield of detecting AF by repeating two sequences of Zio Patch has been reported.[144] Also, it is possible that the study participants who attended visit 6 and underwent continuous monitoring may be healthier than those who did not. When we compared the two groups, those who underwent continuous monitoring were slightly younger, more likely to be white, and have less heart failure and better kidney function and albuminuria; however, were very similar otherwise (**Table B-12**). The cross-sectional design of this study is certainly not a limitation for examining the two-week prevalent burden of arrhythmias; nonetheless, due to the study design, we

cannot establish any temporality in the associations between CKD and arrhythmias. We also could not examine the duration of episodes for most arrhythmias as we did not have access to this information; however, future studies consider examining this in addition to the frequency of episodes to better understand the relationships. Despite the limitations, the strength of our study is that we were able to address important gaps and limitations in the literature by examining various arrhythmias and the different types of arrhythmic burden in association with CKD severity using both eGFR and albuminuria.

In conclusion, the presence of major arrhythmias, specifically, AF and non-sustained ventricular tachycardia, are higher among individuals with more severe CKD. Those with worse CKD also had a higher frequency of long pause and ventricular ectopy. Using a novel 2-week monitoring approach, our study found a broader range of arrhythmias associated with CKD than previously reported.

Table 1. Baseline characteristics by chronic kidney disease (CKD) status

Characteristics	Total	CKD status			
		No CKD	CKD with moderate risk	CKD with high risk	CKD with very high risk
	n=2257	n=945	n=678	n=391	n=243
Age, years (SD)	79.1 (4.6)	77.8 (3.8)	79.4 (4.6)	80.5 (5.0)	81.2 (4.9)
Female, %	56.7	57.6	57.4	56.8	51
Black, %	23.5	22.2	24.0	23.5	27.2
Study center, %					
Forsyth County, NC	22.8	22.1	23.9	23.3	21.8
Jackson, MS	21.9	20.6	22.4	22	25.1
Minneapolis, MN	29	34.1	28.2	22.3	22.6
Washington County, MD	26.3	23.2	25.5	32.5	30.5
Education, %					
< High school	12	8.4	11.9	16.9	18.5
High school graduate	41.5	40.1	42.3	44.2	40.3
College or graduate school	46.5	51.5	45.7	38.9	41.2
Body mass index, kg/m^2 (SD)	28.3 (5.3)	27.3 (4.6)	28.8 (5.3)	29.4 (5.9)	29.5 (5.8)
Current cigarette smoker, %	7.0	6.8	7.5	5.9	8.6
Current drinker, %	51.6	60.1	48.4	43	41.2
Systolic blood pressure, mmHg (SD)	134.9 (18.8)	133.3 (18.2)	135.2 (18.2)	135.8 (18.8)	138.8 (21.9)
Antihypertensive medication, %	76.3	66.2	78.2	87	93.4
Diabetes, %	33.4	25.1	35.8	37.9	51.4
Prevalent cardiovascular disease, %	23.8	17.2	22.4	32.5	39.5
Heart failure, %	12.5	8.3	10.5	18.2	25.4
Coronary heart disease, %	14.0	10.2	12.7	19.5	23.8
Stroke, %	4.4	3.1	3.4	7.2	7.9
Medication for arrhythmia, %	8.9	7.2	9.7	11.5	9.5
QT-prolonging medication, %	10.4	9.4	9.3	12.5	14.0
Total cholesterol, SI Units (SD)	4.5 (1.0)	4.6 (1.0)	4.5 (1.0)	4.4 (1.0)	4.4 (1.1)
High-density lipoprotein, SI Units (SD)	1.3 (0.4)	1.4 (0.4)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
eGFR, ml/min/1.73m^2 (SD)	58.4 (18.3)	74.2 (11.4)	55.7 (9.8)	42.1 (7.5)	31.1 (9.7)
Albumin-to-creatinine ratio, mg/g (IQI)	7.1 (3.5, 18.5)	5.0 (3.0, 9.4)	7.1 (3.3, 17.9)	9.7 (4.2, 31.2)	89.2 (31.4, 338.1)

Total analyzable time, days (IQI)	13.7 (12.7, 13.9)	13.7 (12.8, 13.9)	13.7 (12.8, 13.9)	13.7 (12.1, 13.9)	13.7 (12.4, 13.9)

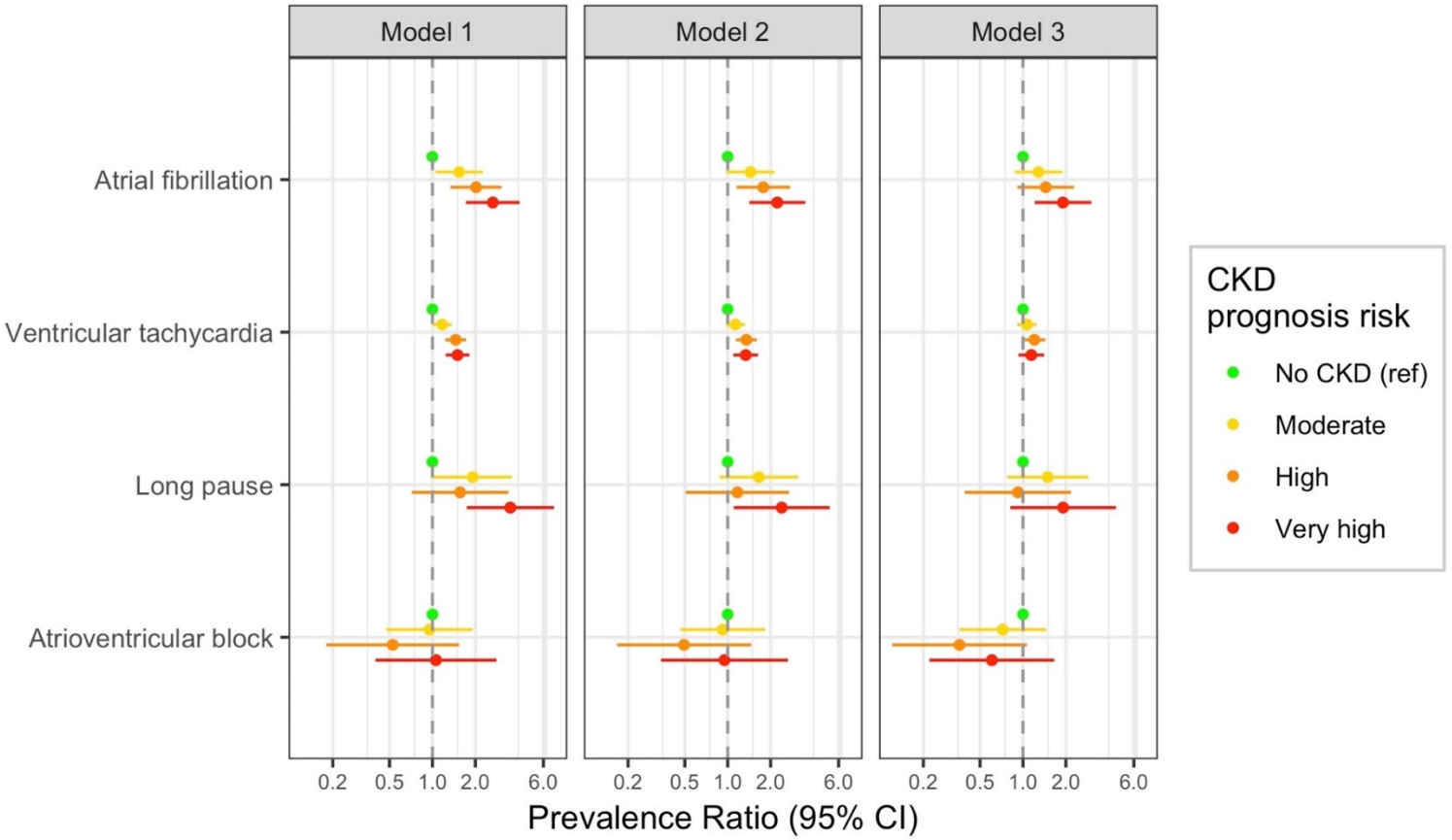
Table 2. Burden of major and minor arrhythmias by chronic kidney disease (CKD) status

Characteristics	Total	CKD status			
		No CKD	CKD with moderate risk	CKD with high risk	CKD with very high risk
	n=2257	n=945	n=678	n=391	n=243
Major arrhythmias					
Atrial fibrillation					
Presence, %	7.4	5.0	7.7	9.7	12.8
Percent of time in arrhythmia (IQI)*, %	100 (5, 100)	11 (2, 100)	100 (4, 100)	100 (100, 100)	100 (100, 100)
Non-sustained ventricular tachycardia					
Presence, %	30.2	25.8	30.2	36.3	37.4
Frequency (number of episodes per day [IQI])*	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.3)
Long pause					
Presence, %	2.7	1.7	3.2	2.6	5.8
Frequency (number of episodes per day [IQI])*	0.2 (0.1, 1.4)	0.2 (0.1, 0.7)	0.2 (0.1, 1.3)	0.1 (0.1, 1.5)	0.5 (0.1, 5.4)
Atrioventricular block					
Presence, %	1.8	2.0	1.9	1.0	2.1
Frequency (number of episodes per day [IQI])*	0.2 (0.1, 0.7)	0.1 (0.1, 0.5)	0.4 (0.1, 0.7)	0.7 (0.4, 0.9)	0.2 (0.1, 0.3)
Minor arrhythmias					
Ventricular ectopy					
Presence, %	98.8	98.6	99.0	99.0	99.2
Frequency (number of episodes per day [IQI])*	68.8 (11.4, 421.7)	53.5 (7.9, 340.9)	70.4 (12.6, 429.9)	80.3 (15.7, 470.2)	122.3 (21.0, 642.3)
Supraventricular tachycardia[§]					
Presence, %	89.8	91.3	89.3	90.0	83.9
Frequency (number of episodes per day [IQI])*	0.9 (0.4, 2.3)	0.9 (0.4, 2.2)	0.8 (0.3, 2.1)	0.9 (0.3, 2.1)	0.9 (0.4, 2.3)
Supraventricular ectopy[§]					
Presence, %	99.9	99.8	100	99.7	100
Frequency (number of episodes per day [IQI])*	202.0 (62.9, 804.6)	170.8 (58.5, 727.0)	206.1 (63.5, 765.4)	230.6 (67.5, 831.4)	291.7 (87.8, 1368.3)

*Characteristics are summarized only among participants with presence of the corresponding arrhythmia

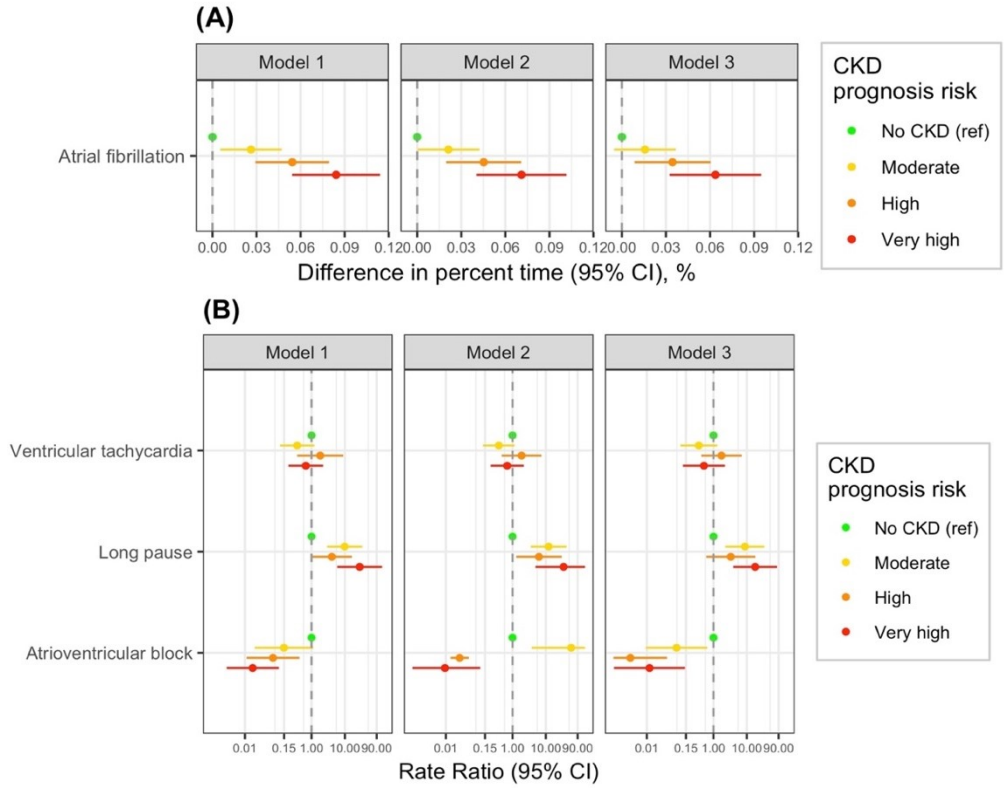
[§]Among participants who do not have continuous atrial fibrillation

Figure 1. Associations of chronic kidney disease (CKD) status with prevalence of major arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

Figure 2. Associations of chronic kidney disease (CKD) status with (A) percent time in atrial fibrillation and (B) frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block



(A) Association of CKD status with percent time in atrial fibrillation; (B) Association of CKD status with frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block
Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

Chapter 3. Cardiac biomarkers, electrolytes, and burden of arrhythmias by chronic kidney disease status: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background: Chronic kidney disease (CKD) increases the risk of arrhythmias and sudden cardiac death; however, it is unclear whether this association is due to cardiac overload, cardiac injury, electrolyte abnormalities, and/or anemia. We therefore investigated the relationships between several biomarkers representing these conditions with various arrhythmias in individuals with CKD.

Methods: In 2016-17, 2233 ARIC participants (71-94 years) underwent 2-week continuous heart rhythm monitoring (Zio XT Patch). We used modified Poisson regression to examine the associations of natriuretic peptide (NT-proBNP) (representing cardiac overload), high-sensitivity cardiac troponin-T (hs-cTnT) (cardiac injury), potassium and magnesium (electrolyte abnormalities), and hemoglobin (anemia) with the burden of arrhythmias captured over a 2-week period: atrial fibrillation (AF), non-sustained ventricular tachycardia (NSVT), long pause (>3 sec), Mobitz II or complete atrioventricular block (AVB), ventricular ectopy (VE), and supraventricular tachycardia (SVT) and ectopy (SVE). We analyzed CKD (n=1300) and no-CKD separately.

Results: There were 9% with AF, 33% with NSVT, 3% with long pause, 2% with AVB, and >90% with VE, SVT, and SVE in CKD. NT-proBNP was associated with all major arrhythmias except for AVB in CKD (prevalence ratio [95%CI] per 2-fold increment 1.82 [1.66, 1.99] for AF; 1.15 [1.10, 1.20] for NSVT). hs-cTnT was also associated with AF and NSVT but the relationships were weaker. In general, the associations were similar in non-CKD. Electrolytes were associated with some arrhythmias, but not consistently between CKD and no-CKD (AF associated with lower potassium in CKD and with lower magnesium in non-CKD). Hemoglobin was not robustly associated with any arrhythmias.

Conclusions: Of the biomarkers tested, cardiac biomarkers showed most robust associations with arrhythmias, followed by potassium and magnesium. Our results suggest cardiac overload and injury as key contributors or markers of high arrhythmia burden in older adults.

Introduction

Chronic kidney disease (CKD) is known as a risk factor of sudden cardiac death and atrial fibrillation.[9,59] In addition, a few studies have reported that CKD may also be associated with other arrhythmias such as bradycardia.[13,134] Given the limited treatment options to improve kidney function and the progressive nature of CKD, the identification of risk factors or markers of arrhythmias in persons with CKD is important. Specifically,

those factors can guide risk-centered prevention and management of arrhythmias (e.g., pacemaker), or shed light on potential preventive and therapeutic targets of arrhythmias in this high-risk population.

There are several potential mechanisms linking CKD to elevated risk of arrhythmias such as cardiac overload and injury, electrolyte disturbance, and anemia. Of these, electrolyte abnormality has been most widely investigated. Indeed, several studies have reported that abnormal levels of potassium or magnesium predict sudden cardiac death or arrhythmias such as ventricular tachycardia or atrial fibrillation.[27,146-152] However, to our knowledge, bradycardia has not been studied in this regard. Also, data regarding the contribution of cardiac overload or injury and anemia to various types of arrhythmias are lacking.

We therefore examined the associations of cardiac biomarkers (natriuretic peptide, a marker of cardiac stress, and cardiac troponin T [cTnT], a marker of cardiac damage), electrolytes (potassium and magnesium), and hemoglobin with the burden of various arrhythmias based on two-week monitoring in individuals with CKD from a large cohort of community-dwelling older individuals. To evaluate whether the associations of these biomarkers are unique to individuals with CKD, we also analyzed participants without CKD as well.

Methods

Study design

The Atherosclerosis Risk in Communities (ARIC) study[47] recruited 15,792 participants in visit 1 (1987-89) from four U.S communities (Forsyth County, NC, Jackson, MS, Minneapolis, MN, and Washington County, MD) and followed them up for 6 subsequent visits (visit 2 in 1990-92, visit 3 in 1993-95, visit 4 in 1996-98, visit 5 in 2011-13, visit 6 in 2016-17, and visit 7 2018-19). In addition, participants were contacted annually (semi-annually beginning in 2012) to provide updated information on medical history. In visit 6, 4,003 participants attended the study examination including assessment of cardiovascular disease, cognitive function, and their risk factors, biospecimen collection, medication review, and a two-week electrocardiogram (ECG) monitoring. Of the 4,003 participants, we excluded participants without the wearable ECG patch data (i.e., those who were ineligible due to pacemakers, implantable cardioverter defibrillators, or skin allergy to adhesive tape [n=323], those who did not agree to wear the device [n=1,030], and those whose devices were lost or returned without data [n=34]); participants who were missing CKD measures (n=194) and missing biomarker values (n=33); those who were not white or black (n=6); and those were missing covariates of interest (n=150). The final analytical sample therefore included 2,233 participants (**Figure C-1**). The ARIC Study was approved by the institutional review board of each participating institution, and written informed consent was obtained from participants at each visit.

Measurement of cardiac biomarkers, electrolytes, and hemoglobin

Cardiac biomarkers were measured using blood samples collected at visit 6. N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of cardiac stress or overload,[153] was measured in EDTA plasma using an electrochemiluminescent immunoassay on a Roche Cobas e411 analyzer (Roche Diagnostics, Indianapolis, IN). The laboratory inter-assay coefficients of variation (CVs) for NT-proBNP were 9.9% at a mean concentration of 41.8 pg/mL, 4.8% at a mean concentration of 151.9 pg/mL and 4.3% at a mean concentration of 4824.1 pg/mL. High sensitivity cTnT (hs-cTnT), a marker of cardiac damage,[154] was measured using the same method with CVs of 9.6% at a mean concentration of 9 ng/L, 5.7% at a mean concentration of 27.1 ng/L and 4.8% at a mean concentration of 2230 ng/L.

Potassium was measured in serum by an indirect ion-selective electrode (ISE) method on Roche C501 Chemistry analyzer (Roche Diagnostics, Indianapolis, IN). The inter-assay CVs were 2.0% and 1.3% at mean concentrations of 3.24 mmol/L and 4.55 mmol/L, respectively. Magnesium was measured in serum, lithium heparin plasma, or urine using a colorimetric method on the Roche Cobas 6000 analyzer (Roche Diagnostics) with CVs of 3.5% and 1.9% at mean concentrations of 1.82 mg/dL and 3.44 mg/dL, respectively. Hemoglobin was measured in EDTA whole blood that has been previously frozen for up to 9 weeks using a Sysmex XS-1000i (Sysmex America, Inc.,

Lincolnshire, IL) with CVs of 0.6-0.8% at mean concentrations ranging from 5.73-16.95 g/dL.

Arrhythmia assessment

The arrhythmias were detected using the Zio XT Patch (iRhythm Technologies Inc., San Francisco, CA), which is a Food and Drug Administration (FDA)-approved ECG skin patch that allows continuous monitoring of arrhythmias for up to 14 days.[16] The Zio Patch has been shown to detect more arrhythmic episodes than the standard Holter monitor and is more comfortable to wear long-term.[16] The ECG data were processed and analyzed using a FDA-approved algorithm, and validated by technicians. The following arrhythmias were detected and included in this study: *major types* including atrial fibrillation, non-sustained ventricular tachycardia, long pause lasting >3 seconds, and Mobitz type II or third-degree atrioventricular block; and *minor types* including ventricular ectopy (premature ventricular contraction), supraventricular tachycardia (not including atrial fibrillation), and supraventricular ectopy.

The primary arrhythmia burden of interest was the presence of each arrhythmia during the two-week monitoring period. The continuous monitoring allowed us to additionally examine the frequency of episodes, which was defined as the number of episodes recorded per day. For atrial fibrillation, however, we examined the percent time

in arrhythmia instead of frequency, as the burden of chronic atrial fibrillation would not be appropriately reflected by frequency of episodes.

We used only the Zio Patch data to ascertain arrhythmia cases in this study because when we used hospitalization records to capture a few additional arrhythmia events in this study, the associations of our interest remained very similar (data not shown).

Covariate measurement

All covariates of interest were measured at visit 6 with the exception of educational background, which was measured at visit 1 and categorized as basic (i.e., less than high school), intermediate (i.e., graduated from high school), or advanced (i.e., college or professional degrees). Age, sex, and race were self-reported. Body mass index was calculated by dividing measured weight by height squared (kg/m^2). Current cigarette smoking and alcohol drinking were self-reported (yes vs. no). Systolic blood pressure was measured in a sitting position after 5-minutes of rest using a validated automatic sphygmomanometer (OMRON HEM-907 XL), and the averaged value of the second and third reading was used. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, use of medication for diabetes, or self-reported physician diagnosis of diabetes. Prevalent cardiovascular disease included adjudicated cases of coronary heart disease, heart failure, and stroke prior to visit 6. Total and high-

density lipoprotein (HDL) cholesterol concentrations were measured using an enzymatic method and the Olympus HDL-Cholesterol test.[140] Use of antihypertensive medication in the past 4 weeks was recorded using self-reported data and review of medication containers when possible. Antiarrhythmic medication was also recorded by inspecting drug containers, and for some antiarrhythmic medications that have overlapping indications (e.g., beta-blockers that may also be used for hypertension or heart failure), we used self-report data to classify the medication accordingly. Using a similar method, commonly-used QT-prolonging medications were also identified (**Table C-1**), as these medications can also affect the risk of arrhythmias.

CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or urinary albumin-creatinine ratio (ACR) ≥30 mg/g.[136] eGFR was calculated using the CKD-EPI equation based on cystatin C,[137] which was measured in serum using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (Roche Diagnostics). We used cystatin C rather than serum creatinine, as there is concern that age-related reduced muscle mass can overestimate eGFR in older individuals when using creatinine.[138] ACR was calculated by dividing urine albumin by urine creatinine. Urine albumin was measured in urine on the ProSpec nephelometric analyzer using an immunoturbidometric method (Dade Behring GMBH. Marburg, Germany), and urine creatinine was measured by a creatinase enzymatic method on a Roche Modular P Chemistry Analyzer (Roche Diagnostics).

Statistical analysis

The distributions of all variables were examined and summarized using mean with standard deviation for normally distributed variables; median with interquartile interval for non-normally distributed variables; and frequency with percentage for categorical variables.

The associations of cardiac biomarkers, electrolytes, and hemoglobin with the presence of arrhythmias were assessed using Poisson regression with robust variance, taking into account the device wear-time as the offset variable. The associations of cardiac biomarkers, electrolytes, and hemoglobin with the number of episodes were modeled using a zero-inflated Poisson regression to accommodate a large proportion of zeroes in the data. To avoid unreliable estimates due to too few episodes, we restricted our analysis of the number of episodes to arrhythmias with average frequency of >0.14 episodes/day (at least 2 episodes over 14 days) in the entire study population. With this criterion, atrioventricular block was excluded from this analysis examining the number of episodes. The associations of all biomarkers with percent time in atrial fibrillation were examined using linear regression. For all associations, we accounted for the following potential confounders: age, sex, race, study center, education, body mass index, current smoking, alcohol use, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total cholesterol, HDL, and antiarrhythmic medications, and QT-prolonging medications, and CKD.

To examine whether the associations in our primary analysis are unique to CKD, we repeated the analysis in non-CKD. We also checked for statistical interactions between CKD status and all biomarkers using a likelihood ratio test.

All analyses were performed in R 3.5.1 and Stata/SE 15.1 (StataCorp, College Station, TX). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among the 2,233 participants, the mean age was 79 (SD 5) years, and the majority were female (56%) and white (76%); taking antihypertensive medication (76%); and had CKD (58%) (**Table 1**). Individuals with CKD were older and less educated, had higher body mass index and systolic blood pressure, were more likely to have diabetes and cardiovascular disease (i.e., heart failure, coronary heart disease, and stroke), and more likely to take antihypertensive, antiarrhythmic, and QT prolonging medications. In terms of biomarkers, those with CKD had significantly higher levels of NT-proBNP and hs-cTnT, similar levels of potassium and magnesium, and lower hemoglobin levels (**Table 1**).

The presence of major types of arrhythmias including atrial fibrillation, ventricular tachycardia, and long pause was higher among CKD compared to no CKD,

whereas the presence of minor arrhythmias was similar (**Table C-2**). Similarly, when we compared other measures of arrhythmia burden, we found that the percent time in atrial fibrillation was higher in CKD, as well as the frequency (i.e., number of episodes per day) of ventricular and supraventricular ectopy (**Table C-2**).

Major arrhythmias

NT-proBNP was associated with the presence of most major arrhythmias in CKD, and the associations were similar in non-CKD (**Table 2**). Among CKD, higher levels of NT-proBNP was significantly associated with higher prevalence of atrial fibrillation, ventricular tachycardia, and long pause (prevalence ratio [PR] for atrial fibrillation 1.82 [95% CI: 1.66, 1.99], PR for ventricular tachycardia 1.15 [1.10, 1.20], PR for long pause 1.30 [1.10, 1.53] per 2-fold higher NT-proBNP in CKD). Atrioventricular block was not strongly associated with NT-proBNP. When we examined other types of arrhythmia burden, the relationships remained similar (**Table 3**).

Similar to NT-proBNP, hs-cTnT was associated with the presence of atrial fibrillation and ventricular tachycardia, but it was not associated with long pause (**Table 2**). When other types of arrhythmia burden were examined in CKD, hs-cTnT remained associated with percent time in atrial fibrillation. In comparison, among no-CKD, higher levels of hs-cTnT were associated with lower frequency of ventricular tachycardia (P for interaction between CKD and hs-cTnT <0.001) and higher frequency of long pause

(**Table 3**). When we looked at the inverse association between hs-cTnT and ventricular tachycardia carefully in no-CKD, actually, there was a reverse J-shaped association, with the highest frequency in the lowest quartile of hs-cTnT and a slight increase in frequency along with hs-cTnT levels in the remaining quartiles (**Table C-3**).

When we estimated prevalence ratio of major arrhythmias between CKD and no CKD across the entire range of NT-proBNP, CKD had higher prevalence ratio of atrial fibrillation, non-sustained ventricular tachycardia, and long pause than non-CKD unless NT-proBNP was around 300 pg/ml (**Figure 1A-C**). Above this range, non-CKD had similar or even higher prevalence ratio than CKD. There was no evident difference between CKD and non-CKD in AV block (**Figure 1D**). Generally, similar patterns were seen for hs-cTnT although the gradient of prevalence ratio appeared shallower than NT-proBNP except AV block (**Figure 1E-H**).

Potassium levels (their decrement below 4.1 mmol/l) were only associated with the presence of atrial fibrillation and no other major arrhythmias in CKD (PR 2.76 [1.38, 5.55] per -1 mmol/l) (**Table 2**). There were no significant associations in non-CKD. In higher levels above 4.1 mmol/l, we observed a lower frequency of ventricular tachycardia in CKD (**Table 3**).

Magnesium was also associated with a limited number of arrhythmias. Among CKD, higher magnesium levels above 2 mg/dl was associated with a higher prevalence of

long pause (**Table 2**). Among non-CKD, lower magnesium levels below 2 mg/dl was associated with a higher prevalence of and percent time in atrial fibrillation (**Tables 2 and 3**). Higher magnesium levels were associated with higher frequency of ventricular tachycardia among non-CKD (**Table 3**).

Hemoglobin demonstrated no statistically significant relationships with the presence, percent time, or frequency of major arrhythmias (**Tables 2 and 3**).

Minor arrhythmias

The presence of minor arrhythmias was not associated with any biomarkers except for ventricular ectopy, which was associated with NT-proBNP only in CKD (**Table 4**). The frequencies of minor arrhythmias, however, were associated with a few biomarkers. In both CKD and no-CKD, there was a higher frequency of ventricular and supraventricular ectopy with higher NT-proBNP levels; and there was a lower frequency of supraventricular ectopy with higher magnesium levels (**Table 5**). Other associations involving the frequency of minor arrhythmias were more inconsistent across CKD status: in CKD, supraventricular tachycardia was less frequent with higher magnesium level, and in no-CKD, supraventricular tachycardia was less frequent with lower hemoglobin while supraventricular ectopy was more frequent with higher hs-cTnT and lower potassium levels, respectively.

Discussion

In community-dwelling older adults, among the biomarkers tested, we found that cardiac biomarkers were most strongly associated with the burden of various major arrhythmias (such as atrial fibrillation) in CKD and no CKD (**Table C-4**). Of the two cardiac biomarkers examined, NT-proBNP demonstrated stronger relationships than hs-cTnT in general. Electrolytes were associated with a limited number of major arrhythmias, with inconsistent results between CKD and no CKD. For example, atrial fibrillation was associated with lower potassium in CKD but with higher magnesium levels in no-CKD. Hemoglobin did not demonstrate strong associations with major arrhythmias. There were less evident associations of the minor arrhythmias with biomarkers than the major arrhythmias. The positive associations of NT-proBNP with ventricular and supraventricular ectopy and the inverse associations of higher levels of magnesium with supraventricular ectopy were present in both CKD and no CKD.

Similar to past studies,[28-31] we found that NT-proBNP and hs-cTnT were strongly associated with the prevalence of atrial fibrillation in CKD and no-CKD. Additionally, we were able to corroborate past findings that the cardiac biomarkers were also associated with higher percent time in atrial fibrillation. Although the directionality of the relationships could not be established in our study, the robust link between these cardiac markers and atrial fibrillation is not surprising since the release of NT-proBNP and hs-cTnT can increase as a result of cardiac stress and damage due to atrial fibrillation. The higher levels of these cardiac markers can reflect cardiac abnormality preceding the

development of atrial fibrillation.[28,33,38] Our results indicate NT-proBNP and hs-cTnT as robust blood markers reflecting high risk status for atrial fibrillation.

The associations of NT-proBNP and hs-cTnT with ventricular tachycardia in the general population are novel. Previous studies were restricted to select patient populations (i.e., those with preexisting ventricular premature complex, implantable cardioverter defibrillator, left ventricular assist device, or systemic sclerosis).[32-37] Like atrial fibrillation, elevated levels of NT-proBNP and hs-cTnT may reflect either or both of cardiac abnormality predating non-sustained ventricular tachycardia or cardiac overload/damage due to this arrhythmia.

We found a consistent association between NT-proBNP and the burden of long pause, which has never been reported to our knowledge. Overall, epidemiologic studies investigating bradycardia are scarce although a case report showed elevated NT-proBNP levels in a patient with junctional escape rhythm due to sinus arrest.[155]

We found that lower levels of potassium were associated with a higher presence (but not necessarily percent time) of atrial fibrillation in CKD. This relationship has been previously observed in population-based cohorts and among those receiving dialysis treatments.[41,151] In addition, we found that higher levels of potassium above 4.1 mmol/l associated with lower rate ratio of non-sustained ventricular tachycardia and its lower levels below this range with a higher frequency of ventricular ectopy in CKD. However, these associations were not consistent when we studied the presence of these arrhythmias and were not seen in non-CKD. These results should be interpreted cautiously.

Magnesium exhibited associations with some arrhythmias. Of those, there were two relationships that were consistent across different arrhythmias or CKD status. Specifically, lower magnesium levels were associated with higher prevalence and percent time of atrial fibrillation in non-CKD and higher levels of magnesium were associated with lower rate ratio of supraventricular ectopy in both CKD and no-CKD. Although we are unsure of the exact underlying mechanisms behind these observations, the importance of magnesium in cardiac arrhythmias has been recognized (e.g., magnesium deficiency prolonging QT duration).[156,157] Nonetheless, epidemiological data regarding magnesium and arrhythmias are limited, and thus future studies are needed.

Contrary to our hypothesis, lower hemoglobin was not associated almost all arrhythmias tested, except for lower frequency of supraventricular tachycardia in no-CKD. This lack of associations of hemoglobin with arrhythmias in our study is in line with a previous study showing no association between chronic anemia and new-onset atrial fibrillation in community-dwelling older adults.[158]

Our findings overall have a few clinical and research implications. Our findings suggest cardiac remodeling and myocardial injury as critical factors for increased risk of arrhythmias in CKD and emphasize the importance of cardiac biomarkers as a potential method of monitoring and managing risks of severe arrhythmias. For example, natriuretic peptide levels may guide clinical decision making of arrhythmia prevention and management (e.g., ICD implantation) in CKD, although this theory should be tested in future studies. In addition, clinical trials could be designed to enroll individuals with high

levels of NT-proBNP or hs-TnT to test if therapies which could modify cardiac overload such as more aggressive lowering of blood pressure as shown in the SPRINT trial would reduce arrhythmias.[159] Our findings also highlight the importance of elucidating the temporality of associations between cardiac overload or injury and the risk of arrhythmias for better understanding the etiology of high-risk arrhythmias in CKD population.

In addition to the cross-sectional design, there are other limitations in our study. Some misclassification of arrhythmias by the continuous ECG monitoring device is possible; however, as the Zio Patch and its arrhythmia-detecting algorithm are FDA-approved for clinical use, this concern remains minimal. Our study population consisted of older, relatively healthy individuals who attended the study visit and underwent two-week ECG monitoring. Consequently, our findings may not be generalizable to younger or sicker individuals. It is also possible that some inconsistent or weak associations that we observed by CKD status were due to small sample sizes of subgroups, limited number of episodes of some arrhythmias, or the result of multiple testing.

In conclusion, our study demonstrates that cardiac biomarkers, especially NT-proBNP, were more consistently associated with the burden of many arrhythmias including atrial fibrillation, non-sustained ventricular tachycardia, and long pause compared to electrolytes and hemoglobin. Our findings suggest that cardiac overload and injury are likely the key contributors or markers associated with the high burden of major arrhythmias in CKD among older adults. Future studies are warranted to further quantify

the temporality of their associations with the development of tachy- and brady-arrhythmias.

Table 1. Baseline characteristics by chronic kidney disease (CKD) status

Characteristics	Total n=2233	No CKD n=933	CKD n=1300
Age, years (SD)	79.2 (4.6)	77.8 (3.8)	80.1 (4.8)
Female, %	56.7	57.7	56.1
White, %	76.5	77.9	75.5
Study center, %			
Forsyth County, NC	22.8	22.2	23.2
Jackson, MS	21.9	20.5	22.8
Minneapolis, MN	29	34.1	25.3
Washington County, MD	26.4	23.3	28.6
Education, %			
< High school	12.1	8.4	14.8
High school graduate	41.6	40.2	42.5
College or graduate school	46.4	51.4	42.7
Body mass index, kg/m^2 (SD)	28.3 (5.3)	27.3 (4.6)	29.1 (5.6)
Current cigarette smoker, %	7.1	6.9	7.2
Current drinker, %	51.5	60.3	45.2
Systolic blood pressure, mmHg (SD)	134.9 (18.7)	133.3 (18.1)	136.0 (19.1)
Antihypertensive medication, %	76.4	66.5	83.5
Diabetes, %	33.2	24.9	39.2
Prevalent cardiovascular disease, %	23.8	17.3	28.5
Heart failure, %	12.5	8.3	15.5
Coronary heart disease, %	14	10.2	16.7
Stroke, %	4.4	3.1	5.3
Medication for arrhythmia, %	9	7.3	10.2
QT-prolonging medication, %	10.4	9.4	11.2
Total cholesterol, SI Units (SD)	4.5 (1.0)	4.6 (1.0)	4.4 (1.0)
High-density lipoprotein, SI Units (SD)	1.3 (0.4)	1.4 (0.4)	1.3 (0.3)
eGFR, ml/min/1.73m^2 (SD)	58.3 (18.3)	74.1 (11.4)	47.0 (13.3)
Albumin-to-creatinine ratio, mg/g (IQI)	7.1 (3.5, 18.3)	5.0 (3.0, 9.4)	10.5 (4.2, 37.6)
N-terminal pro-B-type natriuretic peptide, pg/ml (IQI)	143.0 (72.9, 300.9)	107.0 (57.5, 189.6)	192.7 (90.0, 415.0)
High sensitivity cardiac troponin T, ng/l (IQI)	12.0 (9.0, 18.0)	10.0 (7.0, 13.0)	14.0 (10.0, 21.0)
Serum potassium, mmol/l (IQI)	4.1 (3.9, 4.3)	4.1 (3.9, 4.3)	4.1 (3.9, 4.4)
Serum magnesium, mg/dl (IQI)	2.0 (1.9, 2.1)	2.0 (1.9, 2.1)	2.0 (1.9, 2.1)

Hemoglobin, g/dl (IQI)	13.4 (12.4, 14.4)	13.6 (12.8, 14.5)	13.1 (12.1, 14.2)

Table 2. Association of all biomarkers with prevalence of major arrhythmias by chronic kidney disease status

Biomarkers		Arrhythmias			
		Atrial fibrillation	**Non-sustained ventricular tachycardia**	**Long pause**	**Atrioventricular block**
		Prevalence Ratio (95% CI)			
Chronic kidney disease					
NT-proBNP, per 2-fold		**1.82 (1.66, 1.99)**	**1.15 (1.10, 1.20)**	**1.30 (1.10, 1.53)**	1.10 (0.87, 1.39)
hs-cTnT, per 2-fold		**1.24 (1.01, 1.52)**	**1.14 (1.04, 1.25)**	1.10 (0.76, 1.60)	1.53 (0.99, 2.33)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	**2.76 (1.38, 5.55)**	1.30 (0.87, 1.93)	2.61 (0.76, 8.93)	1.98 (0.49, 8.06)
	>4.1 mmol/l, per 1 mmol/l	0.83 (0.36, 1.95)	0.92 (0.65, 1.30)	0.34 (0.08, 1.46)	0.43 (0.07, 2.61)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	1.04 (0.58, 1.85)	0.95 (0.73, 1.25)	1.25 (0.52, 3.02)	1.08 (0.28, 4.15)
	>2 mg/dl, per 0.5 mg/dl	0.52 (0.21, 1.30)	0.73 (0.48, 1.11)	**3.88 (1.04, 14.49)**	0.71 (0.04, 14.21)
Hemoglobin, per -1 g/dl		0.97 (0.89, 1.05)	0.97 (0.93, 1.01)	0.97 (0.84, 1.11)	1.02 (0.83, 1.25)
No chronic kidney disease					
NT-proBNP, per 2-fold		**2.49 (2.06, 3.01)**	**1.21 (1.13, 1.30)**	**1.77 (1.20, 2.62)**	0.90 (0.66, 1.24)
hs-cTnT, per 2-fold		**2.03 (1.42, 2.90)**	**1.19 (1.02, 1.39)**	1.17 (0.57, 2.40)	0.81 (0.40, 1.63)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	1.87 (0.38, 9.12)	1.30 (0.73, 2.30)	3.09 (0.31, 30.30)	1.11 (0.07, 17.03)
	>4.1 mmol/l, per 1 mmol/l	2.19 (0.33, 14.42)	1.20 (0.71, 2.02)	0.44 (0.02, 11.47)	0.04 (0.00, 6.01)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	**3.08 (1.34, 7.08)**	1.10 (0.68, 1.78)	2.51 (0.73, 8.58)	1.28 (0.27, 5.97)
	>2 mg/dl, per 0.5 mg/dl	2.79 (0.71, 10.94)	1.14 (0.63, 2.08)	0.76 (0.03, 19.65)	0.89 (0.11, 7.54)
Hemoglobin, per -1 g/dl		0.94 (0.78, 1.14)	0.96 (0.90, 1.02)	1.20 (0.83, 1.75)	1.06 (0.81, 1.39)

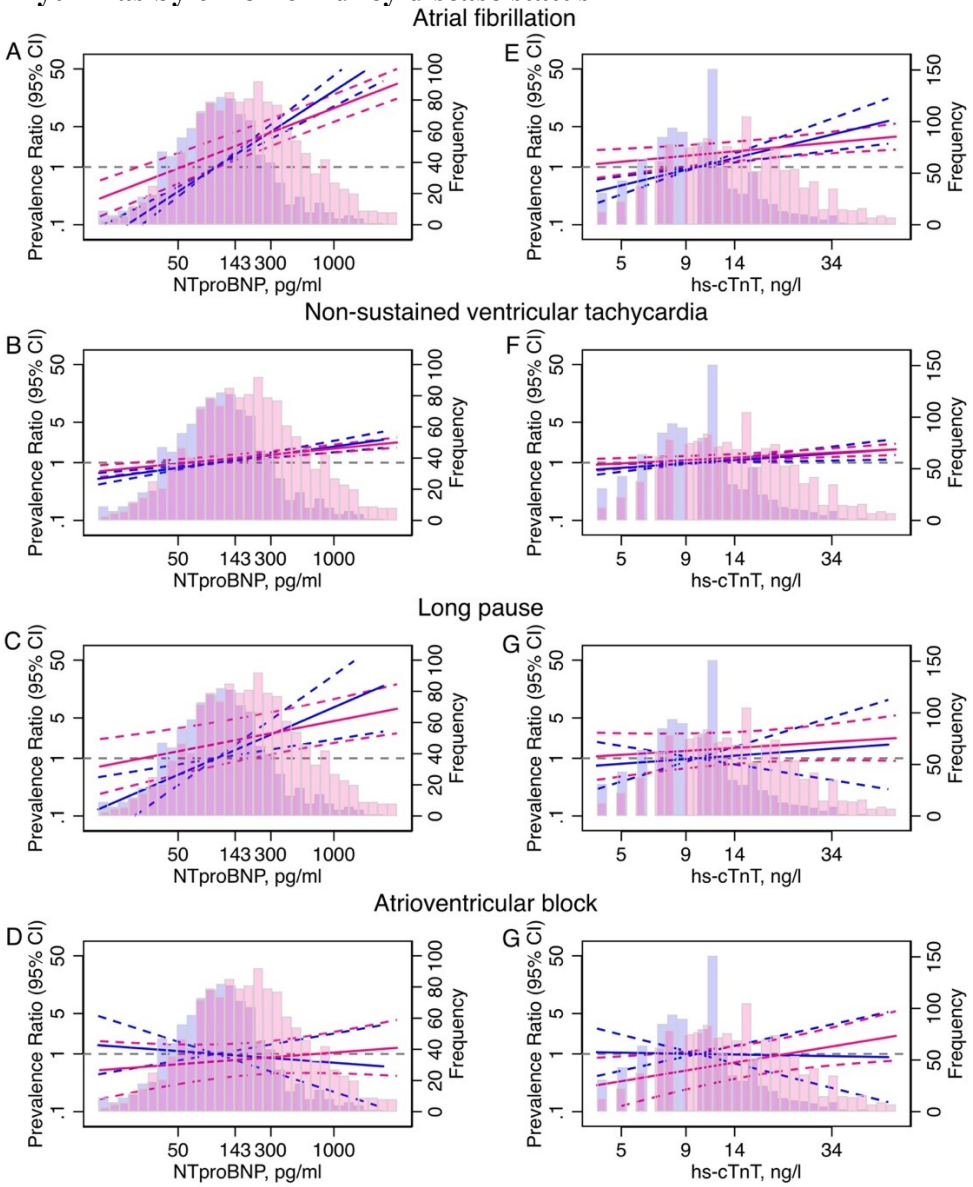
Models adjusted for age, sex, race, study center, education, body mass index, current smoking status, current drinking status, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging medication

Table 3. Association of all biomarkers with percent time and frequency of major arrhythmias by chronic kidney disease status

Biomarkers		Arrhythmias		
		Atrial fibrillation	**Non-sustained ventricular tachycardia**	**Long pause**
		Difference in percent time (95% CI)	Rate Ratio (95% CI)	
Chronic kidney disease				
NT-proBNP, per 2-fold		**0.06 (0.05, 0.07)**	**1.29 (1.12, 1.50)**	**1.36 (1.02, 1.82)**
hs-cTnT, per 2-fold		**0.01 (0.00, 0.03)**	1.76 (0.97, 3.19)	0.95 (0.53, 1.71)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	0.05 (-0.01, 0.11)	0.02 (0.00, 1.00)	0.27 (0.01, 4.99)
	>4.1 mmol/l, per 1 mmol/l	-0.01 (-0.06, 0.04)	**0.02 (0.00, 0.79)**	0.04 (0.00, 3.45)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	0.01 (-0.04, 0.05)	0.67 (0.09, 5.19)	3.35 (0.99, 11.35)
	>2 mg/dl, per 0.5 mg/dl	-0.04 (-0.10, 0.02)	1.12 (0.42, 3.02)	3.03 (0.60, 15.24)
Hemoglobin, per -1 g/dl		-0.00 (-0.01, 0.00)	1.09 (0.94, 1.26)	0.79 (0.58, 1.09)
No chronic kidney disease				
NT-proBNP, per 2-fold		**0.04 (0.03, 0.05)**	**1.31 (1.09, 1.59)**	**2.79 (1.81, 4.28)**
hs-cTnT, per 2-fold		0.01 (-0.01, 0.03)	**0.17 (0.03, 0.86)**	**2.05 (1.01, 4.14)**
Potassium	**<4.1 mmol/l, per -1 mmol/l**	0.03 (-0.04, 0.10)	0.52 (0.12, 2.31)	0.93 (0.12, 6.99)
	>4.1 mmol/l, per 1 mmol/l	-0.01 (-0.08, 0.05)	0.04 (0.00, 7.28)	0.45 (0.00, 57.15)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	**0.08 (0.02, 0.15)**	0.25 (0.01, 5.33)	8.32 (0.82, 84.22)
	>2 mg/dl, per 0.5 mg/dl	0.05 (-0.02, 0.13)	**17.86 (1.85, 172.74)**	1.93 (0.03, 138.35)
Hemoglobin, per -1 g/dl		0.00 (-0.01, 0.01)	0.85 (0.66, 1.10)	0.96 (0.56, 1.65)

Models adjusted for age, sex, race, study center, education, body mass index, current smoking status, current drinking status, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging medication

Figure 1. Associations of NT-proBNP and hs-cTnT with prevalence of major arrhythmias by chronic kidney disease status



A), E) Prevalence ratio for atrial fibrillation; B), F) Prevalence ratio for non-sustained ventricular tachycardia; C), G) Prevalence ratio for long pause; D), H) Prevalence ratio for atrioventricular block; Blue lines and bins represent non-CKD; Pink lines and bins represent CKD; NT-proBNP and hs-cTnT are log-transformed to the base of 2; Reference for NT-proBNP set at 6.7 log-pg/ml in no CKD, and for hs-cTnT, at 3.3 log-ng/l in no CKD

Table 4. Association of all biomarkers with prevalence of minor arrhythmias by chronic kidney disease status

Biomarkers		Arrhythmias		
		Ventricular ectopy (Isolated, couplet, or triplet)	**Supraventricular tachycardia**	**Supraventricular ectopy (Isolated, couplet, or triplet)**
		Prevalence Ratio (95% CI)		
Chronic kidney disease				
NT-proBNP, per 2-fold		**1.01 (1.00, 1.02)**	1.02 (0.99, 1.03)	1.01 (0.99, 1.02)
hs-cTnT, per 2-fold		1.02 (0.99, 1.04)	0.99 (0.96, 1.02)	1.02 (0.99, 1.04)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	0.99 (0.90, 1.08)	1.00 (0.89, 1.13)	0.97 (0.89, 1.06)
	>4.1 mmol/l, per 1 mmol/l	0.99 (0.92, 1.07)	0.98 (0.89, 1.09)	0.95 (0.90, 1.01)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	1.11 (0.99, 1.23)	1.00 (0.85, 1.16)	1.09 (0.98, 1.21)
	>2 mg/dl, per 0.5 mg/dl	1.04 (0.96, 1.13)	1.00 (0.88, 1.13)	1.02 (0.94, 1.11)
Hemoglobin, per -1 g/dl		1.00 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)
No chronic kidney disease				
NT-proBNP, per 2-fold		1.00 (0.98, 1.01)	1.02 (0.99, 1.04)	1.00 (0.98, 1.01)
hs-cTnT, per 2-fold		1.00 (0.98, 1.03)	1.02 (0.98, 1.05)	1.00 (0.97, 1.02)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	1.02 (0.94, 1.11)	1.01 (0.88, 1.15)	1.05 (0.96, 1.15)
	>4.1 mmol/l, per 1 mmol/l	0.99 (0.92, 1.07)	0.93 (0.82, 1.04)	1.00 (0.93, 1.08)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	1.00 (0.94, 1.05)
	>2 mg/dl, per 0.5 mg/dl	0.98 (0.91, 1.06)	1.00 (0.88, 1.12)	1.01 (0.93, 1.08)
Hemoglobin, per -1 g/dl		1.00 (0.99, 1.01)	0.99 (0.98, 1.01)	1.00 (0.99, 1.01)

Models adjusted for age, sex, race, study center, education, body mass index, current smoking status, current drinking status, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging medication

Table 5. Association of all biomarkers with frequency of minor arrhythmias by chronic kidney disease status

Biomarkers		Arrhythmias		
		Ventricular ectopy (Isolated, couplet, or triplet)	**Supraventricular tachycardia**	**Supraventricular ectopy (Isolated, couplet, or triplet)**
		Rate Ratio (95% CI)		
Chronic kidney disease				
NT-proBNP, per 2-fold		**1.36 (1.23, 1.51)**	1.08 (0.87, 1.33)	**1.17 (1.09, 1.26)**
hs-cTnT, per 2-fold		1.21 (0.99, 1.47)	1.02 (0.84, 1.25)	1.13 (0.93, 1.36)
Potassium	**<4.1 mmol/l, per -1 mmol/l**	0.76 (0.35, 1.62)	0.30 (0.05, 1.62)	0.76 (0.40, 1.47)
	>4.1 mmol/l, per 1 mmol/l	1.19 (0.50, 2.82)	0.62 (0.13, 2.87)	0.99 (0.51, 1.92)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	1.42 (0.92, 2.19)	0.30 (0.08, 1.12)	0.84 (0.53, 1.33)
	>2 mg/dl, per 0.5 mg/dl	0.73 (0.29, 1.81)	**0.11 (0.03, 0.38)**	**0.32 (0.16, 0.63)**
Hemoglobin, per -1 g/dl		1.07 (0.98, 1.16)	1.05 (0.86, 1.28)	0.96 (0.86, 1.07)
No chronic kidney disease				
NT-proBNP, per 2-fold		**1.32 (1.16, 1.50)**	1.21 (0.84, 1.74)	**1.15 (1.00, 1.31)**
hs-cTnT, per 2-fold		1.23 (0.93, 1.62)	0.92 (0.47, 1.79)	**1.32 (1.04, 1.68)**
Potassium	**<4.1 mmol/l, per -1 mmol/l**	**3.56 (1.34, 9.45)**	0.81 (0.40, 1.64)	0.73 (0.26, 2.11)
	>4.1 mmol/l, per 1 mmol/l	1.21 (0.19, 7.72)	0.96 (0.31, 2.92)	1.03 (0.47, 2.26)
Magnesium	**<2 mg/dl, per -0.5 mg/dl**	0.83 (0.31, 2.27)	0.28 (0.03, 3.02)	0.84 (0.24, 2.96)
	>2 mg/dl, per 0.5 mg/dl	0.95 (0.40, 2.24)	1.06 (0.10, 11.61)	**0.28 (0.10, 0.77)**
Hemoglobin, per -1 g/dl		1.01 (0.89, 1.15)	**0.79 (0.68, 0.91)**	0.95 (0.84, 1.08)

Models adjusted for age, sex, race, study center, education, body mass index, current smoking status, current drinking status, systolic blood pressure, antihypertensive medication, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging medication

Chapter 4. Diurnal patterns of intermittent atrial fibrillation by chronic kidney disease status: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background: Atrial fibrillation (AF) represents an overwhelming economic burden; however, most studies examined the presence or incidence of atrial fibrillation as a dichotomous outcome, and the diurnal patterns of AF and how these may vary by major comorbid conditions like chronic kidney disease (CKD) status have not yet been characterized.

Methods: We examined 67 participants from the ARIC Study who had intermittent AF in 2-week non-invasive continuous heart rhythm monitoring using the Zio XT Patch. We characterized the probability of AF onset over the course of 24 hours using a generalized multilevel function-on-scalar regression model in CKD (reduced kidney function or elevated albuminuria) and no-CKD.

Results: The median device wear-time was 13.7 (IQI 12.6-13.9) days, and 40 participants had CKD. There was a biphasic pattern of AF with a peak occurring around midnight and a nadir around noon. The highest and lowest probability of AF were 11.4% and 7.8%, respectively, in CKD, and 6.2% and 3.1%, respectively, in no-CKD. Those with CKD had a constantly higher presence of AF throughout day compared to no-CKD, and the

largest and smallest difference was observed around 9pm (odds ratio [OR] 3.28, 95% CI: 1.69, 7.33) and 3am (OR 1.99, 95% CI: 1.18, 3.64). There was a similar level of fluctuation in the diurnal patterns by CKD status.

Conclusions: In community-dwelling older adults, intermittent AF exhibits a biphasic diurnal pattern with a peak occurring around midnight and a nadir around noon regardless of CKD status. Compared to no-CKD, those with CKD have a constantly elevated probability of AF throughout the day, with the greatest difference occurring around 9pm. Further studies are needed to evaluate clinical implications of diurnal variation of intermittent AF.

Introduction

Atrial fibrillation affects more than 5 million Americans annually, and this figure is projected to grow to 12 million by 2030.[160] Atrial fibrillation represents an overwhelming economic burden with an annual medical cost ranging from US$6 to $26 billion,[160] and is strongly associated with cardiovascular disease (CVD) and mortality.[161,162] Yet, despite the high burden, most studies on atrial fibrillation have mainly examined the binary presence or incidence of atrial fibrillation, and to date, only a handful number of studies have explored the diurnal patterns of intermittent atrial fibrillation, which is important to consider as this can have meaningful implications on detection and management of atrial fibrillation.

Past studies that examined the diurnal patterns of atrial fibrillation reported some consistent and inconsistent results on the timing of peaks and nadirs, and had significant caveats in data collection (monitoring only for 24-hour or with a transtelephonic ECG relying on patient action triggered by symptoms), study population (patients with implantable devices), and methods (investigating only the first episodes and treating all episodes within the same individual as independent uncorrelated events).[42-46] Moreover, data regarding whether diurnal patterns vary by the presence and absence of comorbidities like chronic kidney disease (CKD) are scarce.[44]

To overcome these caveats, using data from a two-week continuous ECG patch in a community-based cohort of older adults, we sought to characterize the diurnal patterns of intermittent atrial fibrillation and assess whether they vary by CKD status. We selected CKD as a comorbidity of interest in this study because atrial fibrillation is especially prevalent in individuals with CKD.[9,41,163,164] As the importance of chronobiology in cardiovascular pathophysiology has been described previously (e.g., blood pressure),[40] findings from this study may provide unique insights on strategies to optimize the detection and management of atrial fibrillation. For example, high-risk time windows, if any, can potentially inform the optimal timing of ECG monitoring or treatment strategy for atrial fibrillation (e.g., timing of antiarrhythmic medication use).

Methods

Study design

This study used data from visit 6 (2016-2017) of the ARIC study, which was originally designed to investigate the natural history of atherosclerotic disease from mid- to late-life and has been described previously.[47] Briefly, 15,792 participants were recruited from four communities in the U.S. (Forsyth County, NC, Jackson, MS, Minneapolis, MN, and Washington County, MD) and completed the first study visit (visit 1) during 1987-1989. Since then, there have been six study visits (visit 2 in 1990-1992; visit 3 in 1993-1995; visit 4 in 1996-1998; visit 5 in 2011-2013; visit 6 in 2016-2017; visit 7 in 2018-2019). In addition to these visits, the participants were contacted annually (semi-annually beginning in 2012) for us to obtain updated information on their medical history and lifestyle. In visit 6, 4,003 participants attended the study examination which included a two-week continuous ECG monitoring, biospecimen collection, and assessment for cardiovascular disease, cognitive function, and medications. The ARIC study was approved by the institutional review board of each participating center, and written informed consent was obtained from participants at each study visit.

Study population

Of 4,003 participants who attended visit 6, there were 2,616 participants who underwent two-week ECG monitoring after excluding those who had pacemakers, implantable cardioverter defibrillators, or skin allergy to adhesive tape (n=323), those who did not agree to wear the device (n=1,030), and those whose devices were lost or returned without data (n=34) (**Figure D-1**). There were 67 participants who had

intermittent atrial fibrillation defined as the occurrence of atrial fibrillation over the monitoring period that did not persist for the entire duration of device wear time. For this analysis, we excluded participants who were missing CKD measures (n=194) and who were non-white and non-black (n=6). Our final analytical sample therefore included 67 participants with intermittent atrial fibrillation.

Atrial fibrillation measurement

Atrial fibrillation was measured using the Zio XT Patch (iRhythm Technologies Inc., San Francisco, CA), which is a Food and Drug Administration (FDA)-approved ECG skin patch that is single-lead, non-invasive, lightweight, and water-resistant, and allows ECG recording for up to 14 days.[16] The Zio Patch is demonstrated to detect more arrhythmic events and shown to be more comfortable to wear than the standard 24-hour Holter monitor.[16] Study participants were asked to wear the Zio Patch for up to 14 days and mail the device back to the manufacturer who analyzed the ECG recordings using a FDA-approved proprietary algorithm. For this analysis, we used episodic data, which were comprised of every episode of atrial fibrillation per participant, including the date and time of onset and termination for each episode.

Chronic kidney disease measurement

CKD was defined as a combination of values of estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g according to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD

Guideline.[136] eGFR was calculated based on the CKD-EPI equation using cystatin C,[137] which was measured in serum using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (Roche Diagnostics, Indianapolis, IN) with a laboratory inter-assay CV of 6.1% at a mean concentration of 0.94 mg/L. We used a cystatin C based equation rather than one based on serum creatinine, as there is concern that age-related reduced muscle mass can overestimate eGFR in older individuals when using a creatinine-based equation.[138] ACR was calculated by dividing urine albumin by urine creatinine.[139] Urine albumin was measured in urine on the ProSpec nephelometric analyzer using an immunoturbidometric method (Dade Behring GMBH. Marburg, Germany) with a laboratory inter-assay CV of 4.0% at a mean concentration of 19.7 mg/L. Urine creatinine was measured on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a creatinase enzymatic method (Roche Diagnostics, Indianapolis, IN) that yielded a CV of 4.5% at a mean concentration of 17 mg/dL.

Covariate measurement

All variables except education were measured at ARIC study visit 6. Educational attainment was measured at visit 1 and categorized as less than high school, graduated from high school or vocational school, or obtained college or graduate/professional degrees. Body mass index was calculated by body weight (kg) divided by the square of height (m) and dichotomized to $\geq$25 kg/m^2 (overweight/obese) and <25 kg/m^2. Current cigarette smoking and alcohol drinking were self-reported. Diabetes was defined as

fasting plasma glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, using medication for diabetes, or self-reported physician diagnosis of diabetes. Prevalent cardiovascular disease included coronary heart disease, heart failure, and stroke, and these were assessed based on prior events adjudicated by physician reviewers using medical records and/or hospitalization data. Systolic and diastolic blood pressure measures were the average of the last two of three recordings in a sitting position after five minutes of rest using a validated automatic sphygmomanometer (OMRON HEM-907 XL). Antihypertensive medication use in the past 4 weeks was assessed by self-report and confirmed with drug containers. We assessed the use of antiarrhythmic medication in a similar manner and additionally assessed QT-prolonging medications as these are also associated with the risk of arrhythmias. [142] The list of QT-prolonging medications can be found in **Table D-1**).[141]

Statistical analysis

We checked the distributions of all variables and summarized them by CKD status. Continuous variables were described with mean and standard deviation [SD] if normally distributed or with median and interquartile interval [IQI] if non-normally distributed. Categorical variables were summarized using frequency and percentages.

For all analyses, we formatted the data so that the presence of atrial fibrillation was summarized in moving time-windows for each day of the monitoring period with the intention of smoothing over time. After some exploratory analysis, we decided to use a

10-minute time window with 5 minutes of overlap between the windows, hence, we created 288 time windows for each day.

We first performed a series of visual exploratory data analysis to check for crude patterns of atrial fibrillation presence by CKD status. First, for every participant, we visualized the occurrence of atrial fibrillation episodes over all the days of the monitoring period by plotting the time and duration of each episode over 24 hours and by day to roughly inspect any patterns or potential outliers. Second, to visualize a crude (unadjusted) diurnal pattern, we created a probability plot of atrial fibrillation over the course of the day. For this visualization, we first summarized the presence or absence of atrial fibrillation that accumulated over the entire monitoring period of 2 weeks. We then plotted the binary presence of atrial fibrillation over 24 hours, and fit binomial smoothing curves to estimate the probability of being on intermittent atrial fibrillation.

To appropriately characterize the diurnal pattern of atrial fibrillation and how this may differ by CKD status, we analyzed the effect of CKD on the presence of atrial fibrillation over time adjusting for covariates by fitting a generalized multilevel function-on-scalar regression,[165] which involved the following two steps. First, at every time window, we used a generalized estimating equation (GEE) with a logit link function to estimate the marginal effect of CKD as well as other covariates on the binary presence of atrial fibrillation accounting for multiple days per subject and using an exchangeable correlation structure. We generated bootstrapped 95% confidence intervals (CIs) using 1000 resamples at each time window. Then, we smoothed the coefficients and the 95%

CIs from the models as a function of time and plotted the smoothed lines to visualize the patterns over time. We additionally generated and visualized the predicted probabilities of atrial fibrillation to compare those with and without CKD. Due to a small sample size, we only adjusted for age (centered at mean age of 80 years) and sex.

Results

Baseline characteristics

Of 67 participants with intermittent atrial fibrillation, 40 (60%) had CKD. Compared to those without CKD, those with CKD were slightly older, less likely to be black, had higher body mass index and burden of cardiovascular diseases and its risk factors (**Table 1**).

Exploratory data analysis of atrial fibrillation episodes by chronic kidney disease status

Figure 1 illustrates the timing of onset and duration of atrial fibrillation episodes over the course of ECG monitoring by CKD status. In general, we observed that those with CKD had a higher frequency of episodes and longer duration of atrial fibrillation compared to those without CKD.

Figure 2 depicts the crude unadjusted probabilities of atrial fibrillation summarized over all days of the monitoring period. Roughly, in the overall group of participants, atrial fibrillation exhibited a biphasic pattern with higher presence around midnight and had a lower probability of occurring around noon. When examined by CKD status, we found that the general pattern remained similar in the subgroups; however, the

presence of atrial fibrillation was consistently higher among those with CKD than those without CKD.

Diurnal patterns of intermittent atrial fibrillation by CKD status

Based on the generalized estimating equation, we observed similar diurnal variation of the probabilities of atrial fibrillation in both those with and without CKD (**Figure 3**), with a peak at midnight and a nadir around noon. At a given day, the peak probability of atrial fibrillation around midnight was 11.4% in CKD and 6.2% in no-CKD, and the lowest probability around noon was 7.8% in CKD and 3.1% in no-CKD. In this approach, we also observed a few other peaks smaller than the peak at midnight in both CKD and no-CKD (e.g., around 9 am). Also, no-CKD demonstrated a dip around 9 pm. Nonetheless, when comparing the absolute change in the probability of atrial fibrillation over 24 hours, the mean slopes were similar by CKD status (0.0004 [SD 0.0002] per 10 min in CKD vs. 0.0004 [SD 0.0003] per 10 min in no-CKD) (**Figure D-2**), indicating a similar level of fluctuation in the diurnal patterns by CKD status.

Overall, CKD was associated with a significantly higher odds of having an episode of atrial fibrillation throughout the entire day than no-CKD (**Figure 4**). The highest difference in the probability of atrial fibrillation in CKD vs. no-CKD was seen around 9pm (Odds ratio [OR] 3.29, 95% CI: 1.69, 7.33), when no-CKD had a dip of the probability of atrial fibrillation. The smallest difference between CKD status in the presence of atrial fibrillation was observed around 3am (OR 1.99, 95% CI: 1.18, 3.64).

Discussion

Among community-dwelling older adults, we found that intermittent atrial fibrillation exhibited an overall biphasic diurnal pattern with a peak around midnight, and a nadir around noon. The patterns were largely similar regardless of CKD status. Although no-CKD demonstrated a dip of the probability of atrial fibrillation around 9 pm, the overall fluctuation, expressed as the 24-h average of the absolute change in the probability of atrial fibrillation, was not different between CKD and no-CKD. The probability of atrial fibrillation was consistently higher in CKD than in no-CKD throughout the day, but their difference was the largest around 9pm with an OR of 3.29 (95% CI: 1.69, 7.33).

Only a handful number of studies have previously described the diurnal patterns of intermittent atrial fibrillation. All studies[42,44-46,166,167] except one with a transtelephonic ECG[43] reported a peak occurring at night. Of these six studies, five reported a peak around midnight,[42,44-46,167] as in our study. Some of these studies reported additional peaks occurring in the morning or in the afternoon,[42,46,166] and we observed some peaks smaller than the midnight peak in our study as well. Some differences across past studies and our study may reflect differences in study participant characteristics (e.g., age, cardiovascular disease profile, and various indications for undergoing heart rhythm monitoring) and methods of atrial fibrillation ascertainment (e.g., Holter monitor or implantable device). Regarding a nadir, most previous studies reported around noon,[42,44-

[46,166] similarly as our study. Of interest, a few studies also reported a peak termination time of intermittent atrial fibrillation around noon.[42,45,46]

There are a few plausible mechanisms behind diurnal pattern of intermittent atrial fibrillation. Sleep disturbances (including sleep apnea) are known to increase the risk of atrial fibrillation and thus may contribute to the peak around midnight.[168] However, this may be unlikely as the average bedtime in older adults is around this time,[169] although we do not have data on bedtime in our study population. More likely mechanism is a vagal arrhythmogenic activity. Indeed, atrial fibrillation is induced by vagal stimulation,[45] and past studies have characterized the biphasic circadian rhythm of the cardiac autonomic activity, with a peak around midnight and a nadir around noon,[170] which is identical to the overall diurnal pattern of intermittent atrial fibrillation in our study (**Figure 2**). Nonetheless, future studies are needed to better understand biological or pathophysiological mechanisms of the diurnal pattern of atrial fibrillation.

To our knowledge, very few studies have described the diurnal patterns of atrial fibrillation by major comorbid conditions. One study compared the patterns by body mass index (<25, 25-30, and >30 kg/m^2) and found no significant differences.[44] In this study, we found that overall, the shape of the pattern including the level of fluctuation was similar by CKD status. The lack of differences in diurnal pattern of intermittent atrial fibrillation by BMI and CKD may indicate that the diurnal pattern of atrial fibrillation may reflect biological circadian rhythm like autonomic nervous system.

This study has a few clinical and research implications. Based on our finding that atrial fibrillation exhibits a peak around midnight, screening or monitoring for atrial fibrillation should cover nighttime. In this context, at a given duration of monitoring, Holter and Zio XT Patch seem to have advantage over a transtelephonic ECG relying on patient symptom (patient would not be able to recognize palpitation while sleeping) or a watch-type device as some people may not prefer to wear it while sleeping. However, a watch-type device may be able to overcome this caveat by longer wearing time. Our findings may also potentially guide strategies for managing intermittent atrial fibrillation. For example, antiarrhythmic medications are still often used to manage atrial fibrillation, and thus strategies to maintain therapeutic concentration at midnight may be effective. Nonetheless, further studies are first needed to confirm our findings and to better understand the mechanisms and extrinsic factors underlying the diurnal patterns of atrial fibrillation. Furthermore, in light of all of our findings, future studies are needed to understand the prognostic impact of the diurnal patterns of atrial fibrillation. For example, it is unknown whether deviating from known diurnal patterns of atrial fibrillation during specific time windows could translate to a higher or lower risk of adverse outcomes such as stroke (like dipper vs. non-dipper for blood pressure).[171]

A limitation worth noting in our study includes a small sample size that may have limited our statistical power in detecting true differences in diurnal patterns by CKD status. Nonetheless, we were able to detect consistently significant differences in the odds of atrial fibrillation across CKD throughout the day and found consistent diurnal patterns

after accounting for age and sex. Another limitation includes the fact that our analytical sample consisted of mostly white older individuals, which may affect the generalizability of our findings. As diurnal patterns could be influenced by extrinsic lifestyle factors, such as eating schedule, physical activity, and sleep, it is important to consider the characteristics of our population when extending or validating our results to other populations. There is also potential for some misclassification of arrhythmias by the ECG monitoring device; however, as the Zio Patch and its arrhythmia-detecting algorithm are FDA-approved for clinical use, this concern remains minimal. Despite the limitations, using a wearable ECG patch still allowed us to continuously capture atrial fibrillation events over 14 days, which we used to characterize more robust diurnal patterns of atrial fibrillation. Our modeling approach also allowed us to also adjust for important covariates of age and sex, which has not been commonly done in the past.

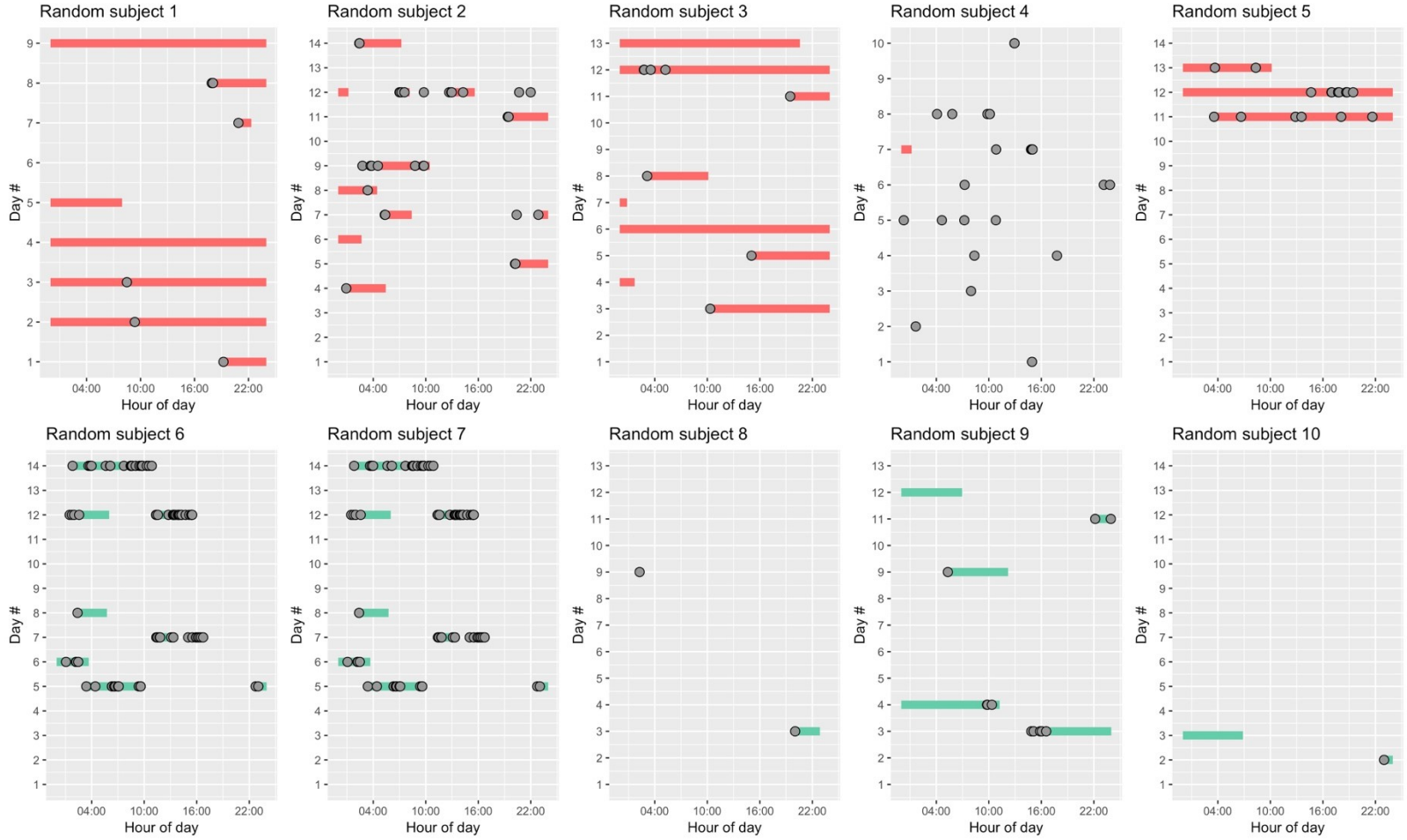
In conclusion, our findings suggest that intermittent atrial fibrillation exhibits an overall biphasic diurnal pattern with a peak occurring around midnight and a nadir around noon in both CKD and no-CKD. Compared to no-CKD, those with CKD have a constantly elevated probability of atrial fibrillation throughout the day, with the greatest difference around 9pm. Future studies are needed to evaluate clinical implications of diurnal variation of intermittent atrial fibrillation.

Table 1. Baseline characteristics of 67 study participants by chronic kidney disease status (CKD)

	CKD N=40	**No CKD** N=27
Mean age (SD), years	80.8 (4.9)	78.9 (3.5)
Female (%)	52.5	51.9
Black (%)	10	11.1
Study center (%)		
Forsyth County, NC	27.5	14.8
Jackson, MS	7.5	7.4
Minneapolis, MN	30	55.6
Washington County, MD	35	22.2
College or equivalent (%)	40	48.1
Mean BMI (SD), kg/m2	29.6 (5.8)	26.7 (4.3)
Current smokers (%)	15.4	7.4
Current drinker (%)	48.7	66.7
Mean systolic BP (SD), mmHg	134.4 (22.7)	134.7 (17.9)
Antihypertensive medication (%)	87.2	69.2
Diabetes (%)	32.5	14.8
Prevalent cardiovascular disease (%)	29.7	11.1
Heart failure (%)	8.1	3.7
Coronary heart disease (%)	25.7	7.4
Stroke (%)	5.4	3.7
Antiarrhythmic medication (%)	25	22.2
QT prolonging medication* (%)	20.5	23.1
Median analysis time (SD), days	13.8 [12.6, 13.9]	13.6 [12.4, 13.8]

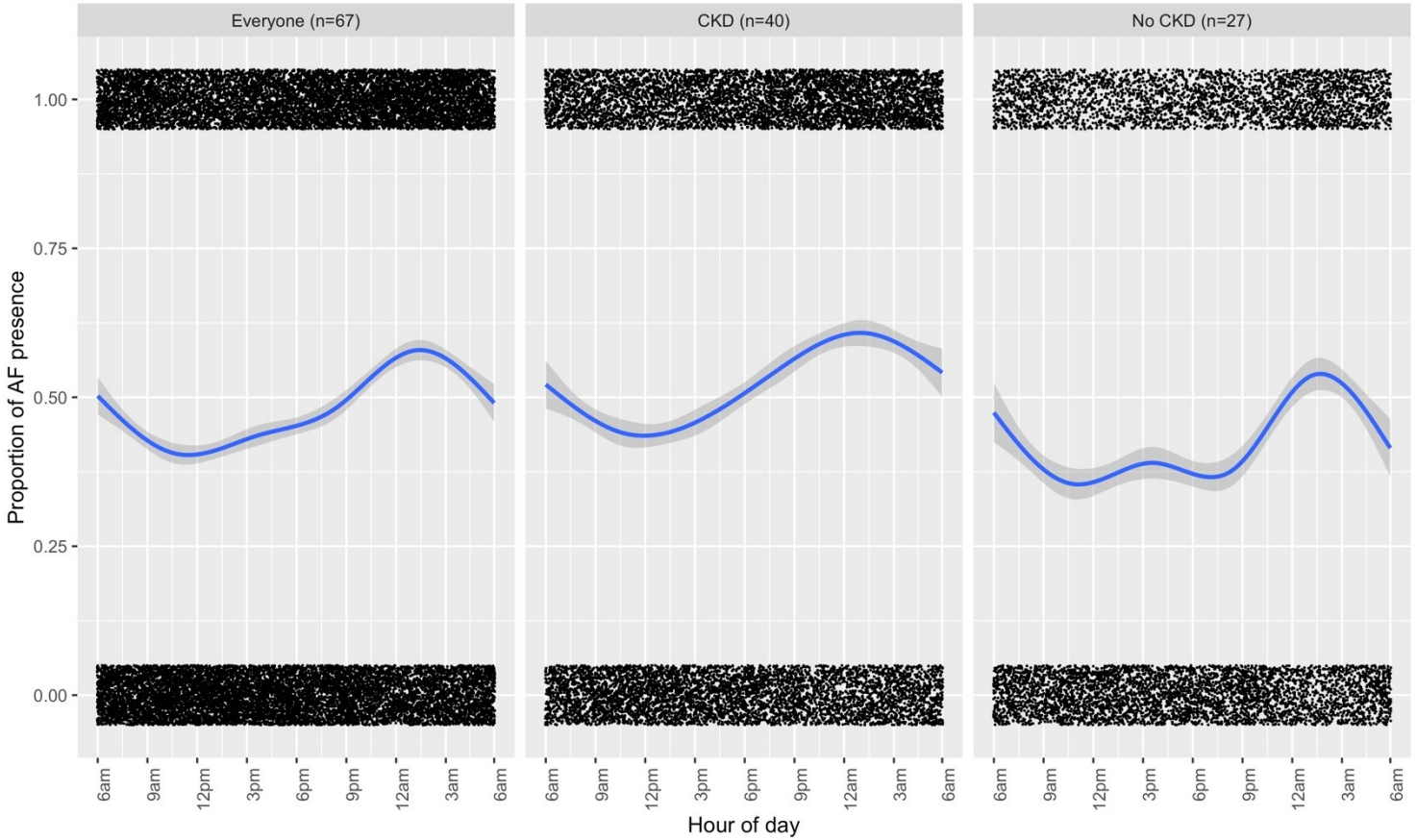
*List of QT prolonging medication listed in **Table D-1**

Figure 1. Plot of atrial fibrillation episode onset (represented by circles) and duration (represented by horizontal bars in red or green) in a random sample of 10 participants with chronic kidney disease (top row displayed in red) and no-CKD (bottom row displayed in green)



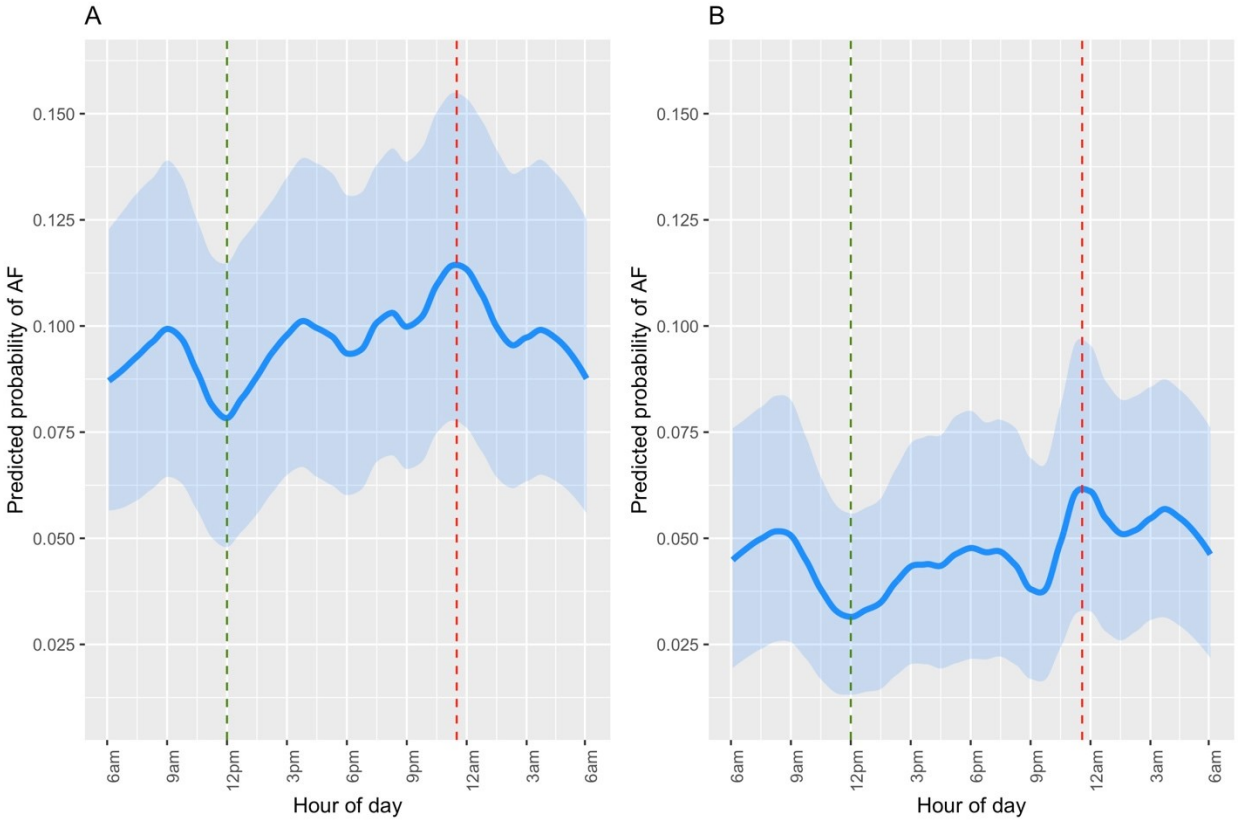
Random subjects 1-5 depicted in red have chronic kidney disease; random subjects 6-10 depicted in green do not have chronic kidney disease

Figure 2. Crude (unadjusted) 24-hour probability plots of atrial fibrillation presence summarized over 14 days



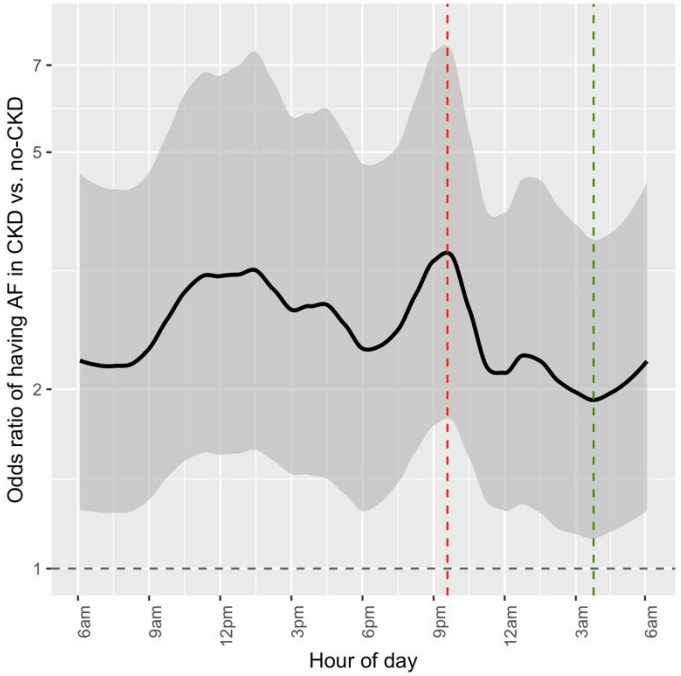
Jittered dots in black represent presence (y=1) or absence (y=0) of atrial fibrillation episodes at a given time

Figure 3. Predicted probability of atrial fibrillation in a given day from GEE models by chronic kidney disease status among males with a mean age of 80 years



A) Chronic kidney disease; B) no chronic kidney disease
Blue shaded area represents bootstrapped 95% confidence interval.
Green dashed line represents the time of minimum predicted probability; red dashed line represents the time of maximum predicted probability.
This model included CKD, age, and sex.

Figure 4. Association of chronic kidney disease with presence of atrial fibrillation over 24 hours



Shaded area in dark grey represents bootstrapped 95% confidence interval.
Red dashed line represents time of maximum difference; green dashed line represents time of minimum difference.

Conclusion

This dissertation investigated critical topics related to the burden of arrhythmias in CKD by leveraging a new wearable ECG patch in a large community-based cohort study. Quantification of disease burden is a vital initial step for acknowledging disease importance and strategizing public health and clinical practice. We thus identified large gaps in knowledge through a systematic review of the literature and addressed the gaps by establishing a crucial knowledge basis of clinically significant arrhythmias in CKD patients. Since there are no established treatments for recovering kidney function, we also identified modifiable risk factors or markers of clinically significant arrhythmias in CKD that would have clinical implications for preventing arrhythmias and identifying individuals at a high risk of arrhythmias with CKD. We lastly characterized the diurnal patterns of AF that may help identify windows of time with high arrhythmic risk which may guide timing of ECG assessment and antiarrhythmic medication administration.

Summary of findings and implications

In *Chapter 1*, we screened 16,245 articles and reviewed and analyzed 58 articles that reported relationships between CKD measures and arrhythmias in diverse study populations. Most studies were prospective and cross-sectional in design, and of high quality. These studies mainly examined AF in relationship with eGFR and demonstrated that lower kidney function was independently associated with a higher risk of AF. Some studies also demonstrated a significant burden of incident life-threatening ventricular

arrhythmias among CKD. Fewer studies examined albuminuria and these mainly focused on the relationship between albuminuria and AF, which was consistent and similar as with eGFR. There were, however, no studies that examined albuminuria with other arrhythmias, and there were only a few studies that examined other types of arrhythmia in the context of CKD.

The robust relationship between CKD and AF is important given the high risk of stroke in CKD.[132] This finding suggests that clinicians should better monitor or manage AF in patients with CKD, and consider optimal methods for screening (e.g., 24-holter or longer monitoring using wearable devices[16]). Moreover, the excess risk of severe ventricular arrhythmias in CKD highlights the need to study arrhythmias beyond AF in CKD. This study also highlights critical gaps in knowledge that future studies should tackle. Specifically, we found that there were limited data on arrhythmias other than AF and ventricular arrhythmia and few studies explored one of the two key kidney measures, albuminuria, in this regard.

Chapter 2 addressed the key knowledge gaps found in *Chapter 1* by analyzing the burden of various arrhythmias as well as the two major kidney measures, eGFR and albuminuria, in a community-based cohort of older individuals. We found a higher prevalence of clinically significant arrhythmias such as AF and non-sustained ventricular tachycardia among those with more severe CKD. AF showed the most consistent association with CKD severity, regardless of the type of burden examined (i.e., the prevalence and percent time in arrhythmia). This study also found that CKD with higher

risk was associated with higher frequency of long pause, which has not been widely reported in past literature. There was also a robust association between CKD and higher frequency of ventricular ectopy. When we examined the two CKD measures, eGFR and ACR, separately, ACR was associated with more arrhythmias overall.

In support of the research conducted in *Chapter 1,* this study also found a robust CKD-AF relationship and corroborated past studies by demonstrating consistent relationships regardless of the arrhythmia burden and CKD measures that were examined, which further highlights the importance of AF management among CKD. This study also adds to the small but growing knowledge base on the relationship between CKD and bradycardia[13,134] and supports the need to pay attention to bradycardia in clinical practice and research in CKD patients. Furthermore, this research strengthens recent statements from the American Heart Association emphasizing the importance of moving beyond examining arrhythmias only as a binary entity.[145] We found that by examining different types of arrhythmia burden, we gained additional insights into the relationships between CKD and various arrhythmias that would have been missed by relying only on the presence vs. absence of arrhythmias.

Chapter 3 tested various cardiac biomarkers (i.e., NT-proBNP and hs-cTnT), electrolytes (i.e., potassium and magnesium), and hemoglobin with the burden of arrhythmias. This study found that the cardiac biomarkers, especially NT-proBNP, were strongly associated with the burden of various arrhythmias in CKD and no-CKD. Compared to cardiac biomarkers, electrolytes were only associated with very few

arrhythmias in CKD. For example, atrial fibrillation was associated with lower potassium in CKD but with higher magnesium levels in no-CKD. Hemoglobin did not demonstrate strong associations with arrhythmias.

This research provides a few implications for future research and clinical practice. This research supports the need for future studies to elucidate the temporality of associations and to better understand the extent to which cardiac overload or injury contribute or mediate the risk of arrhythmias among the high-risk CKD population. The findings also suggest that cardiac overload and injury are key markers of high arrhythmic burden in CKD, which highlights the potential value of cardiac biomarkers guiding targeted monitoring or management of severe arrhythmias in individuals with CKD.

In *Chapter 4*, we identified a biphasic diurnal pattern of intermittent AF. Regardless of CKD status, there was a peak occurring around midnight and a nadir around noon. Compared to no-CKD, those with CKD had a constantly elevated probability of AF throughout the day, with the greatest difference occurring around 9pm.

This research overall suggests that there seems to be a biphasic diurnal pattern of intermittent AF among a small group of community-dwelling older individuals. The peak observed around midnight suggests that monitoring for AF should cover nighttime, in which case, the use of Holter monitors or the Zio XT Patch may be advantageous, as individuals could more easily wear these while sleeping in contrast to perhaps a wearable watch, which some individuals may be not prefer to wear during bedtime. Our findings also have implications for treatment of AF. As AF is often treated using antiarrhythmic

medications, keeping a therapeutic concentration around midnight would be helpful for managing AF. However, further studies are needed to confirm our findings and to better understand the mechanisms and extrinsic factors underlying the diurnal patterns of atrial fibrillation.

Future directions

Prognostic value of ECG patch-detected arrhythmias

First, this dissertation demonstrated that by leveraging a new continuous monitoring ECG patch, we can study various types of arrhythmia that would be difficult to capture using conventional devices due to the transient and asymptomatic nature of arrhythmias. Some examples are long pause and atrioventricular block which are not as commonly occurring as atrial fibrillation or ventricular tachycardia. This dissertation therefore established crucial knowledge base on the burden of different arrhythmia types; however, it will be crucial for future studies to discern the prognostic value of the relationships observed in this research. For example, the association between atrial fibrillation and stroke has been relatively well-studied,[41] but whether lesser-studied arrhythmias also confer higher risk of adverse outcomes such as cardiovascular disease or mortality remains unknown. Furthermore, the wearable ECG patch was able to capture both diagnosed and undiagnosed arrhythmias, thus, future studies will also need to elucidate the prognostic value of undiagnosed or asymptomatic arrhythmias. In this dissertation, we did not distinguish between diagnosed and undiagnosed arrhythmias but

past studies have shown that undiagnosed atrial fibrillation detected through more invasive forms of long-term monitoring is also associated with a higher risk of stroke.[12,14] Therefore, future research are needed to address the prognostic values of ECG patch-detected arrhythmias to better understand the value of continuous monitoring and strategies for prevention and management of arrhythmias in CKD.

Second, this dissertation demonstrated that it is important to consider various aspects of arrhythmia burden and not only examine the binary presence of arrhythmias. With newer continuous monitoring devices that can help measure different measures of arrhythmia burden such as frequency and duration more easily, it will be crucial for future studies to evaluate their prognostic impact to understand the values of these comprehensive measures. For example, in the case of atrial fibrillation, we demonstrated in this research that CKD severity is associated with both the presence of atrial fibrillation and percent time spent in atrial fibrillation. However, the relationships between different measures of atrial fibrillation burden and the risk of an adverse outcome such as stroke are not well-characterized. This will be important to investigate in the future, as current guidelines for stroke prevention in atrial fibrillation do not consider the percent time of atrial fibrillation as a clinical parameter for guiding treatment.[145] Similarly, the prognostic impact of the burden of other types of arrhythmia should be further examined in the future.

Prognostic value of diurnal patterns of arrhythmias

Our research explored the diurnal patterns of intermittent AF and found a biphasic pattern throughout the day. This is an important step in better understanding the burden of atrial fibrillation, as diurnal patterns can highlight the underlying biological mechanisms, such as the role of the autonomic nervous system. Although the circadian rhythm of the cardiac autonomic activity may contribute to the observed diurnal pattern of AF, our study did not examine the potential role of extrinsic factors (e.g., sleep, diet, physical activity); therefore, future studies should also consider the role of various extrinsic factors on the occurrence of AF. In our study, we also could not characterize the diurnal patterns of other arrhythmias due to data availability; however, future studies should build on our work and investigate the diurnal patterns of other clinically significant arrhythmias, as past studies have suggested that ventricular tachycardia/fibrillation and SCD are more likely to occur in the morning and could be sympathetically-driven.[172,173]

Summary

This dissertation established a crucial knowledge basis of clinically significant arrhythmias in CKD, identified key markers of clinically significant arrhythmias in CKD, and characterized the diurnal patterns of atrial fibrillation. Our research further highlights the relevance of arrhythmias in CKD, sheds light on the importance of cardiac overload and injury in the pathophysiology of arrhythmias, and demonstrates a diurnal pattern of AF as an entity with potential clinical implications. This dissertation will guide future

studies in a few aspects: the need to focus on several arrhythmias including bradyarrhytmias in CKD, the importance of further investigating cardiac overload and injury for preventing and managing arrhythmias, and the potential value of diurnal patterns of arrhythmias for guiding clinical management of arrhythmias.

Appendices

Appendix A: Supplementary materials for Chapter 1

Table A-1. Literature search strategy

Chronic kidney disease	Arrhythmia	Study filter
PubMed		
"Kidney Diseases"[Mesh] OR kidney disease*[tw] OR renal disease*[tw] OR "Renal Insufficiency"[Mesh] OR renal insufficienc*[tw] OR kidney insufficienc*[tw] OR “kidney dysfunction”[tw] OR “renal dysfunction”[tw] OR "Dialysis"[Mesh] OR “dialysis”[tw] OR “hemodialysis”[tw] OR “haemodialysis”[tw] OR kidney failure*[tw] OR renal failure*[tw] OR "Uremia"[Mesh] OR “uremia”[tw] OR “ESRF”[tw] OR “ESKF”[tw] OR “ESRD”[tw] OR “ESKD”[tw] OR “CKF”[tw] OR “CKD”[tw] OR “CRF”[tw] OR “CRD”[tw] OR "Creatinine"[Mesh] OR “serum creatinine”[tw] OR “creatinine clearance”[tw] OR "Glomerular Filtration Rate"[Mesh] OR “glomerular filtration rate”[tw] OR “GFR”[tw] OR “eGFR”[tw] OR "Albuminuria"[Mesh] OR “albuminuria”[tw] OR “albumin creatinine ratio”[tw] OR “albumin-to-creatinine ratio”[tw] OR “albumin to creatinine ratio”[tw] OR “albumin/creatinine ratio”[tw] OR “ACR”[tw] OR "Proteinuria"[Mesh] OR “proteinuria”[tw] OR “protein creatinine ratio”[tw] OR “protein-to-creatinine ratio”[tw] OR “protein to creatinine ratio”[tw] OR “protein/creatinine ratio”[tw] OR "beta 2-Microglobulin"[Mesh] OR	"Arrhythmias, Cardiac"[Mesh] OR Arrhythmia*[tw] OR "Atrial Fibrillation"[Mesh] OR “Atrial fibrillation”[tw] OR "Atrioventricular Block"[Mesh] OR Atrioventricular block*[tw] OR Long pause*[tw] OR Long pausing*[tw] OR "Ventricular Premature Complexes"[Mesh] OR ventricular premature complex*[tw] OR ventricular ectop*[tw] OR supraventricular ectop*[tw] OR "Arrhythmogenic Right Ventricular Dysplasia"[Mesh] OR "Torsades de Pointes"[Mesh] OR “torsade de pointes”[tw] OR dysrhythmia*[tw] OR tachyarrhythmia*[tw] OR bradyarrhythmia*[tw] OR "Tachycardia"[Mesh] OR tachycardia*[tw] OR "Bradycardia"[Mesh] OR bradycardia*[tw] OR fibrillation*[tw] OR flutter*[tw] OR premature atrial contraction* [tw] OR premature ventricular contraction* [tw] OR “heart block”[tw] OR "Sick Sinus	("Epidemiologic Studies"[Mesh:NoExp] OR "Observational Study" [Publication Type] OR "Observational Studies as Topic"[Mesh] OR "Cohort Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "epidemiologic study"[tw] OR "epidemiologic studies"[tw] OR cohort*[tw] OR "case control"[tw] OR "observational study"[tw] OR "observational studies"[tw] OR retrospective[tw] OR "cross sectional"[tw])

“beta 2-Microglobulin”[tw] OR “beta-2-microglobulin”[tw] OR “B2M”[tw] OR beta-trace protein*[tw] OR beta trace protein*[tw] OR "Cystatin C"[Mesh] OR “cystatin C”[tw] OR “urine albumin excretion”[tw] OR “urinary albumin excretion”[tw] OR “urine protein excretion”[tw] OR “urinary protein excretion”[tw]	Syndrome"[Mesh] OR “sick sinus syndrome” [tw] OR heart rhythm disorder*[tw] OR heart rhythm abnormalit*[tw]	
Embase		
'renal replacement therapy'/exp OR 'kidney disease'/exp OR 'uremia'/exp OR 'creatinine'/exp OR 'estimated glomerular filtration rate'/exp OR 'glomerulus filtration rate'/exp OR 'albuminuria'/exp OR 'proteinuria'/exp OR 'beta 2 microglobulin'/exp OR 'urine albumin to creatinine ratio'/exp OR 'urine protein to creatinine ratio'/exp OR 'urine protein creatinine ratio'/exp OR 'urine albumin creatinine ratio'/exp OR 'cystatin C'/exp OR 'protein urine level'/exp OR (‘kidney disease*’ OR ‘renal disease*’ OR ‘renal insufficienc*’ OR ‘kidney insufficienc*’ OR 'dialysis' OR 'hemodialysis' OR 'haemodialysis' OR ‘kidney failure*’ OR ‘renal failure*’ OR 'uremia' OR 'esrf' OR 'eskf' OR 'esrd' OR 'eskd' OR 'ckf' OR 'ckd' OR 'crf' OR 'crd' OR 'serum creatinine' OR ‘creatinine clearance’ OR ‘glomerular filtration rate’ OR ‘eGFR’ OR ‘GFR’ OR ‘albuminuria’ OR ‘albumin to creatinine ratio’ OR ‘albumin-to-creatinine ratio’ OR ‘albumin creatinine ratio’ OR ‘albumin/creatinine ratio’ OR ‘ACR’ OR ‘proteinuria’ OR ‘protein creatinine ratio’ OR protein-to-	'heart arrhythmia'/exp OR 'sick sinus syndrome'/exp OR (arrhythmia* OR 'atrial fibrillation' OR ‘atrioventricular block*’ OR ‘long pause*’ OR ‘long pausing*’ OR ‘ventricular ectop*’ OR ‘ventricular premature complex*’ OR ‘supraventricular ectop*’ OR 'torsade de pointes' OR dysrhythmia* OR tachyarrhythmia* OR bradyarrhythmia* OR tachycardia* OR bradycardia* OR fibrillation* OR flutter* OR ‘premature atrial contraction*’ OR ‘premature ventricular contraction*’ OR ‘heart block’ OR ‘sick sinus syndrome’ OR ‘heart rhythm abnormalit*’ OR ‘heart rhythm disorder*’):ab,ti	('epidemiology'/de OR 'community sample'/exp OR 'cohort analysis'/exp OR 'observational study'/exp OR 'retrospective study'/exp OR 'clinical study'/de OR 'case control study'/exp OR 'cross-sectional study'/exp) OR ('case control'):ti,ab OR (cohort NEXT/1 (study or studies or analys*)):ti,ab OR ((observational OR epidemiologic*) NEXT/1 (study OR studies)):ab,ti OR ((retrospective or "cross sectional") AND (study or studies or analys* or cohort*)):ab,ti

creatinine ratio' OR 'protein to creatinine ratio' OR 'protein/creatinine ratio' OR 'beta-2 microglobulin' OR 'beta 2-microglobulin' OR 'B2M' OR 'beta trace protein*' OR 'beta-trace protein' OR 'urine albumin excretion' OR ' urinary albumin excretion' OR 'urine protein excretion' OR 'urinary protein excretion' OR 'Cystatin C'):ab,ti		

Table A-2. Data extraction elements

Heading	Elements
Study details	Author, year, journal, country of origin
Study population	Number of participants, setting, population characteristics, enrollment period, follow-up years
Eligibility criteria	Inclusion criteria, exclusion criteria
Kidney disease measurement	CKD measure, CKD measure categorization
Arrhythmia measurement	Arrhythmia, atrial fibrillation measurement/definition, ventricular tachycardia measurement/definition, ventricular fibrillation measurement/definition, prolonged pause measurement/definition, atrioventricular block measurement/definition, premature atrial contraction measurement/definition, premature ventricular contraction measurement/definition, other arrhythmia measurement/definition, overall number of events
Statistical method	Statistical method
Baseline characteristics	Age, male, race, body mass index, obesity, coronary heart disease, heart failure, stroke, other cardiovascular disease, hypertension, current smoking, systolic blood pressure, diastolic blood pressure, dyslipidemia, total cholesterol, low-density lipoprotein, diabetes, left ventricular ejection fraction, other echocardiographic parameters, eGFR, albuminuria/proteinuria, cystatin C, other CKD measure, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, prolonged pause, atrioventricular block, premature atrial contraction, premature ventricular contraction, other arrhythmia, antihypertensive medication, angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker, beta-blocker, calcium channel blocker, antiplatelet, diuretic, antidiabetic medication, statin, antiarrhythmic medication, implantable cardioverter defibrillator, pacemaker, other arrhythmia therapy
Results	Arrhythmia type, effect estimate without adjustment, effect estimate with adjustment, adjusted variables

Table A-3. Newcastle Ottawa Scales for cohort studies

Newcastle Ottawa Scales for Cohort Studies Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.	
Selection	1) Representativeness of the exposed cohort a) truly representative of the average _____ (describe) in the community * b) somewhat representative of the average _____ in the community * c) selected group of users (e.g. nurses, volunteers) d) no description of the derivation of the cohort 2) Selection of the non-exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non-exposed cohort 3) Ascertainment of exposure a) secure record (e.g. surgical records) * b) structured interview * c) written self report d) no description 4) Demonstration that outcome of interest was not present at start of study a) yes * b) no
Comparability	1) Comparability of cohorts on the basis of the design or analysis a) study controls for _____ (select the most important factor) * b) study controls for any additional factor * (This criterion could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome a) independent blind assessment * b) record linkage * c) self report d) no description 2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow up period for outcome of interest) * b) no

	3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for * b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) * c) follow up rate < ____% (select an adequate %) and no description of those lost d) no statement

Table A-4. Newcastle Ottawa Scales adapted for cross-sectional studies

Selection	1) Representativeness of the sample: a) Truly representative of the average in the target population. * (all subjects or random sampling) b) Somewhat representative of the average in the target population. * (non-random sampling) c) Selected group of users. d) No description of the sampling strategy. 2) Sample size: a) Justified and satisfactory. * b) Not justified. 3) Non-respondents: a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. * b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c) No description of the response rate or the characteristics of the responders and the non-responders. 4) Ascertainment of the exposure (risk factor): a) Validated measurement tool. ** b) Non-validated measurement tool, but the tool is available or described* c) No description of the measurement tool.
Comparability	1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. a) The study controls for the most important factor (select one). * b) The study control for any additional factor. *
Outcome	1) Assessment of the outcome: a) Independent blind assessment. ** b) Record linkage. ** c) Self report. * d) No description. 2) Statistical test: a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). * b) The statistical test is not appropriate, not described or incomplete.

Table A-5. Newcastle Ottawa Scales for case-control studies

Selection	1) Is the case definition adequate? a) yes, with independent validation* b) yes, eg record linkage or based on self reports c) no description 2) Representativeness of the cases a) consecutive or obviously representative series of cases* b) potential for selection biases or not stated 3) Selection of Controls a) community controls* b) hospital controls c) no description 4) Definition of Controls a) no history of disease (endpoint)* b) no description of source
Comparability	1) Comparability of cases and controls on the basis of the design or analysis a) study controls for _____ (Select the most important factor.)* b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)
Exposure	1) Ascertainment of exposure a) secure record (eg surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self report or medical record only e) no description 2) Same method of ascertainment for cases and controls a) yes* b) no 3) Non-Response rate a) same rate for both groups* b) non respondents described c) rate different and no designation

Table A-6. Quality assessment of the 58 studies included in the systematic review using the Newcastle Ottawa Scales

Prospective study					
Reference	**Year**	**Selection/4**	**Comparability/2**	**Outcome/3**	**Total score/9**
Alonso	2011	4	2	3	9
Babu	2016	4	2	3	9
Bansal	2017	4	2	3	9
Deo[§]	2010	4	2	3	9
Eisen	2017	4	2	3	9
Elahi	2003	4	2	3	9
Hage	2011	4	2	2	8
Hai	2017	4	2	3	9
Horio	2010	4	2	3	9
Hreybe	2006	3	2	3	8
Hsu	2013	4	2	3	9
Iguchi	2010	4	2	2	8
Jensen	2013	4	2	3	9
Jensen	2014	4	2	3	9
Khurshid	2018	4	2	3	9
Kreuz	2010	4	2	3	9
Kreuz	2011	4	2	3	9
Laukkanen	2016	3	2	3	8
Lee	2016	4	2	3	9
Liao	2017	4	2	3	9
Liao	2015	4	2	3	9
Lim	2017	4	2	3	9
Marcos	2017	4	2	2	8
Molnar	2017	4	2	3	9
Naruse	2011	4	2	2	8
Nelson	2012	3	2	3	8
Robin	2006	4	2	3	9
Sciacqua	2014	4	2	3	9
Shen	2016	3	2	3	8
Takahashi	2009	4	2	3	9
Tokuda	2011	4	2	2	8
Watanabe	2009	4	2	3	9
Xu	2015	4	2	3	9
Cross-sectional studies					
Reference	**Year**	**Selection/5**	**Comparability/2**	**Outcome/3**	**Total score/10**
Ananthapanyasut	2010	3	2	3	8
Auer	2007	4	2	3	9
Baber	2011	4	2	3	9

Chua	2013	4	2	3	9
Deo[§]	2010	3	2	3	8
Deshmukh	2017	4	2	3	9
Gorczyca-Michta	2013	4	2	1	7
Hashemzadeh	2013	1	2	3	6
Iguchi	2008	4	2	3	9
Karatas	2015	1	2	3	6
Limite	2016	4	2	3	9
Liu	2011	3	2	3	8
McManus	2009	4	2	3	9
Nisanoglu	2007	2	2	3	7
Ohsawa	2016	4	2	3	9
Ohyama	2013	3	2	3	8
Soliman	2010	4	2	3	9
Soman	2002	5	2	3	10
Suzuki	2012	4	2	3	9
Todorov	2017	2	2	3	7
Yonezawa	2018	4	2	3	9
Case-control studies					
Reference	**Year**	**Selection/4**	**Comparability/2**	**Outcome/3**	**Total score/9**
Dalal	2012	4	2	2	8
Liu	2015	3	2	1	6
Lu	2016	3	2	2	7
Mene-Afejuku	2017	3	2	1	6

[§] This study is listed as both prospective and cross-sectional because it includes examinations of incident and prevalent atrial fibrillation

Table A-7. Summary of 21 cross-sectional studies included in the systematic review

Study	Year	Region	N	Population characteristic	Age (mean [SD])	Male, %	Hypertension, %	Current smoking, %	SBP (mean [SD])	CAD, %	HF, %	Stroke, %	Diabetes, %	Follow-up
Cross-sectional studies														
Ananthap-anyasut	2010	USA	1,010	Multicenter-based inpatients and outpatients	65.7 (15.0)	51.5	91.1	32.2	136.0 (19.0)	34.1	30	11.6	59.3	NA
Auer	2007	Austria	253	Single-based patients who underwent elective cardiac surgery	65.0 (11.0)	60.1	62.8	-	-	-	-	-	24.9	NA
Baber	2011	USA	26,917	Population-based	65.2 (9.2)	45.1	58.7	14.5	-	13.2	4.8	-	20.6	NA
Chua	2013	China	265	Single center-based inpatients who underwent cardiac surgery	62.3(9.8)	77	77	43.4	-	-	34	-	54	NA
Deo[§]	2010	USA	4,663	Population-based outpatients	75.3 (5.3)	41.7	41.6	9.7	-	21.6	6	-	15.5	NA
Deshmukh	2017	USA	331	Single center-based patients who underwent LVAD implantation	57.8 (12.8)	77.3	75.5	-	-	-	-	-	49.2	NA
Gorczyca-Michta	2013	Poland	2,512	Single center-based inpatients diagnosed with hypertension	67 (30–89)[†]	54.6	100	-	-	30.4	37.7	5	25.3	NA
Hashemz-adeh	2013	Iran	1,254	Single center-based patients who underwent cardiac surgery	55.1 (15.7)	68.9	8	40.2	-	-	-	3	20.5	NA
Iguchi	2008	Japan	41,417	Population-based	72 (65–78)*	33.7	35.4	26.5	125.7 (16.2)	-	-	-	12.2	NA

Karatas	2015	Turkey	621	Single center-based patients hospitalized with STEMI and treated with PCI	57.0 (11.9)	74.7	41.7	65.9	120.0 (20.0)†	44.4	-	-	19.3	NA
Limite	2016	Italy	444	Single center-based patients who underwent cardiac surgery	60.2 (11.5)	73.6	49.1	11	-	38.6	-	1.6	16.5	NA
Liu	2011	China	451	Single center-based outpatients with hypertension	55.7 (12.0)	49.4	100	25.1	149.7 (27.5)	-	-	-	-	NA
McManus	2009	USA	956	Multicenter-based outpatients with coronary artery disease	66.3 (10.1)	81.5	70.3	-	132.8 (21.0)	-	17	-	26.8	NA
Nisanoglu	2007	Turkey	426	Single center-based patients who underwent CABG surgery	70.1 (4.4)	69.5	41.8	49.5	-	-		1.9	18.5	NA
Ohsawa	2016	Japan	27,964	Combination of population-based cohort and dialysis patients	62.5 (11.6)	36.3	45.7	11.9	131.0 (130.6 – 131.4)‡	-	-	-	7.9	NA
Ohyama	2013	Japan	20,019	Population-based	53.2 (9.2)	62	30.8	26.5	125.7 (16.2)	-	-	-	8	NA
Soliman	2010	USA	3,257	Multicenter-based pre-dialysis chronic kidney disease patients	58.6 (10.8)	54	86	14	-	-	10	-	45	NA
Soman	2002	USA	9,544	Single center-based patients in coronary care unit	63.4 (13.8)	57.8	62.9	-	-	-	-	-	28.9	NA
Suzuki	2012	Japan	1,074	Single center-based outpatients diagnosed	63.5 (12.3)	73.7	47.3	-	-	-	25.7	7.3	18.5	NA

				with atrial fibrillation										
Todorov	2017	Germany	999	Single center-based inpatients who underwent CABG and/or valve surgery	67 (58–75)†	72.1	-	-	-	-	-	-	-	NA
Yonezawa	2018	Japan	108,951	Population-based	56.5 (13.3)	48.2	23.2	37.7	125.8 (17.1)	-	-	-	6.9	NA

* Median with interquartile interval
† Median with interquartile interval or interquartile range among those without atrial fibrillation
‡ Median with interquartile interval among community-dwelling males

Table A-8. Summary of 4 case-control studies included in the systematic review

Study	Year	Region	N	Population characteristic	Age (mean [SD])	Male, %	Hypertension, %	Current smoking, %	SBP (mean [SD])	CAD, %	HF, %	Stroke, %	Diabetes, %	Follow-up
Case-control studies														
Dalal	2012	Netherlands	676	Multicenter-based patients with STEMI	56.9 (11.2)	80.0	28.3	64.9	-	57.4	-	-	76.9	NA
Liu	2015	China	640	Single center-based inpatients and outpatients	68.6 (7.8)	49.5	-	-	141.3 (15.7)	-	-	-	-	NA
Lu	2016	Malaysia	228	Single center-based inpatients with bradyarrhythmias	61.2 (13.3)	68.4	72.4	13.6	134.9 (24.6)	-	-	5.3	46.0	NA
Mene-Afejuku	2017	Nigeria	150	Single center-based hypertensive heart failure patients and healthy controls	63.0 (12.7)	-	-	-	128.9 (25.3)	-	-	-	-	NA

Table A-9. List of covariates adjusted for in prospective studies examining the association between eGFR groups and atrial fibrillation

Study	Year	Adjusted variables
Watanabe	2010	Age, sex, body mass index, systolic blood pressure, diastolic blood pressure, treated hypertension, diabetes
Deo	2010	Age, sex, race, diabetes, C-reactive protein, low-density lipoprotein, high-density lipoprotein, prevalent coronary heart disease, prevalent heart failure, left ventricular hypertrophy, systolic blood pressure, diastolic blood pressure, angiotensin-converting-enzyme inhibitor, beta blocker, calcium channel blocker, diuretic
Horio	2010	Age, smoking, diuretic, left atrial diameter, left ventricular mass index
Alonso	2011	Age, sex, race, study site, education, income, height, smoking, drinking, diabetes, systolic blood pressure, antihypertensive medication, body mass index, high sensitivity C-reactive protein, prevalent coronary heart disease, prevalent heart failure, incident heart failure or myocardial infarction during follow-up, any hospitalization before end of follow-up
Naruse	2011	Age, sex, persistent atrial fibrillation, left atrial volume, left ventricular ejection fraction, left ventricular mass index
Hsu	2013	Age, sex, race, CD4 cell count, HIV RNA viral load, hypertension, diabetes, coronary artery disease, congestive heart failure, chronic lung disease, smoking, alcoholism, hyperthyroidism, hypothyroidism, body mass index, proteinuria
Sciacqua	2014	Smoking, age, hypercholesterolemia, sex, hypertension, diabetes, obesity, metabolic syndrome, left ventricular hypertrophy, left atrial volume index

Xu	2015	Age, sex, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, triglyceride, high-density lipoprotein, smoking, alcohol, diabetes
Laukkanen	2016	Age, sex, examination year, systolic blood pressure, smoking, body mass index, alcohol, diabetes, antihypertensive medication, myocardial infarction, coronary heart disease, heart failure
Molnar	2017	Age, sex, income, index year, diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/ transient ischemic attack, hemorrhage, heart failure, peripheral vascular disease, coronary artery bypass graft
Bansal: JHS	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial fraction, stroke, systolic blood pressure, diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Bansal: MESA	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial fraction, stroke, systolic blood pressure, diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Bansal: CHS	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic blood pressure, diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration

Table A-10. List of covariates adjusted for in prospective studies examining the association between continuous eGFR and atrial fibrillation

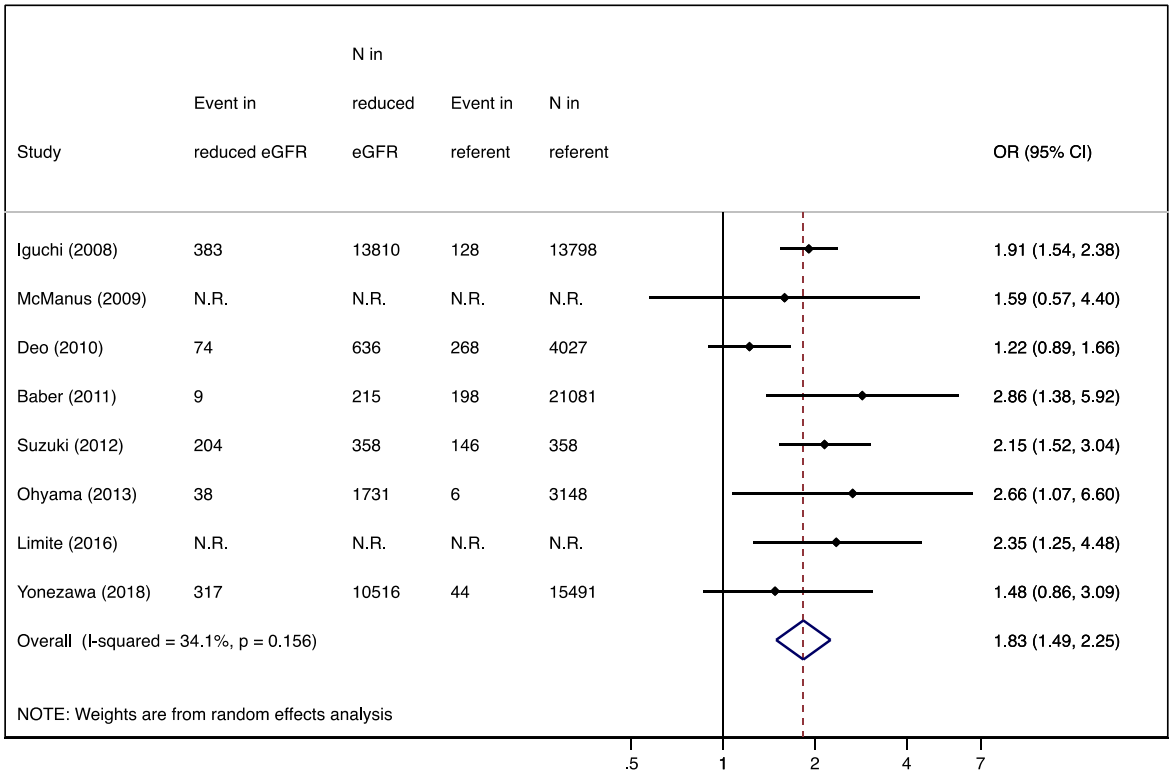
Study	Year	Adjusted variables
Watanabe	2009	Age, sex, body mass index, systolic and diastolic blood pressure, hypertension, diabetes
Iguchi	2010	Age, sex, cardiac disease, diabetes, hypertension, hypercholesterolemia
Tokuda	2011	Hypertension, left atrial diameter
Sciacqua	2014	Smoking, fasting glucose, low-density lipoprotein, age, gender, systolic blood pressure, body mass index, left ventricular mass index, E/A ratio, left atrial volume index
Eisen: No CVD	2017	Age, gender, hypertension, diabetes, chronic obstructive pulmonary disease, beta blockers, angiotensin-converting-enzyme inhibitor, statin
Eisen: With CVD	2017	Age, gender, hypertension, diabetes, chronic obstructive pulmonary disease, beta blockers, angiotensin-converting-enzyme inhibitor, statin, prior cardiovascular disease
Bansal: JHS	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic and diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Bansal: MESA	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic and diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Bansal: CHS	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic and diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Macros	2017	Age, sex, body mass index, antihypertensive, heart failure, previous myocardial infarction, diabetes, peripheral artery disease, smoking, PR interval duration, N-terminal pro b-type natriuretic peptide, interim myocardial infarction, interim heart failure

Table A-11. Summary of cross-sectional study results on the association between eGFR groups and atrial fibrillation

Study	Year	eGFR categorization (ml/min/1.73m^2)	Referent group (ml/min/1.73m^2)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted variables
Baber	2011	≥60 & ACR <30, ≥60 & ACR ≥30, 30-59, <30	≥60 & ACR <30	Not reported	≥60 & ACR ≥30: 2.20 (1.64-2.94), 30-59: 1.51 (1.21-2.05), <30: 2.86 (1.38-5.92)	Age, race, sex, geographic region, current smoking, body mass index, hypertension, diabetes, coronary artery disease, symptoms of heart failure, ECG-detected left ventricular hypertrophy, elevated cholesterol, statin, renin-angiotensin-system inhibitor, CRP ≥3 mg/L
Deo	2010	≥60, <60	≥60	1.92 (1.45-2.56)	1.22 (0.89-1.66)	Age, gender, race, diabetes, C-reactive protein, low and high-density lipoprotein, coronary heart disease, heart failure, left ventricular hypertrophy, systolic and diastolic blood pressure, angiotensin-converting-enzyme inhibitor, beta-blocker, calcium channel blocker, diuretic
Iguchi	2008	>75.5, 62.6-75.5, <62.6	<62.6	Not reported	62.6-75.5: 1.12 (0.88-1.42), <62.6: 1.91 (1.54-2.38)	Age, gender, vascular risk factors, cardiac disease
Limite	2016	≥90, 60-89, <60	≥90	60-89: 1.83 (1.20-2.79), <60: 3.0 (1.67-5.39)	60-89: 1.59 (1.01-2.5), <60: 2.35 (1.25-4.48)	Age, eGFR, combined surgery, arterial hypertension, coronary artery disease
McManus	2009	>85, 66-85, <66	>85	66-85: 1.26 (0.49-3.23), <66: 2.89 (1.27-6.59)	66-85: 1.00 (0.33-3.01), <66: 1.59 (0.57-4.40)	Age, Age^2, gender, race, body mass index, systolic and diastolic blood pressure, hypertension, left ventricular ejection

						fraction, albumin-creatinine ratio
Ohyama	2013	≥90, 60-89, <60	≥90	Not reported	60-89: 1.55 (0.66-3.65), <60: 2.66 (1.07-6.60)	Age, gender, hypertension, diabetes, smoking, cardiac disease, proteinuria
Suzuki	2012	>73.7, 60.1-73.7, <60.1	>73.7	60.1-73.7: 1.49 (1.16-1.91), <60.1: 2.23 (1.74-2.85)	60.1-73.7: 1.71 (1.22-2.41), <60.1: 2.15 (0.79-1.94)	Age, heart failure, organic cardiac disease, valvular heart disease, cardiomyopathy, diabetes, dyslipidemia, cerebral infarction or transient ischemic attack, antiarrhythmic drug class 1 and 4, digitalis, proteinuria
Yonezawa	2018	≥90, 60-89, <60	≥90	Not reported	60-89: 1.48 (0.86-2.77), <60: 1.58 (0.86-3.09)	Age, gender, hypertension, diabetes, smoking

Figure A-1. Odds ratios (ORs) of atrial fibrillation comparing reduced to referent eGFR groups from cross-sectional studies

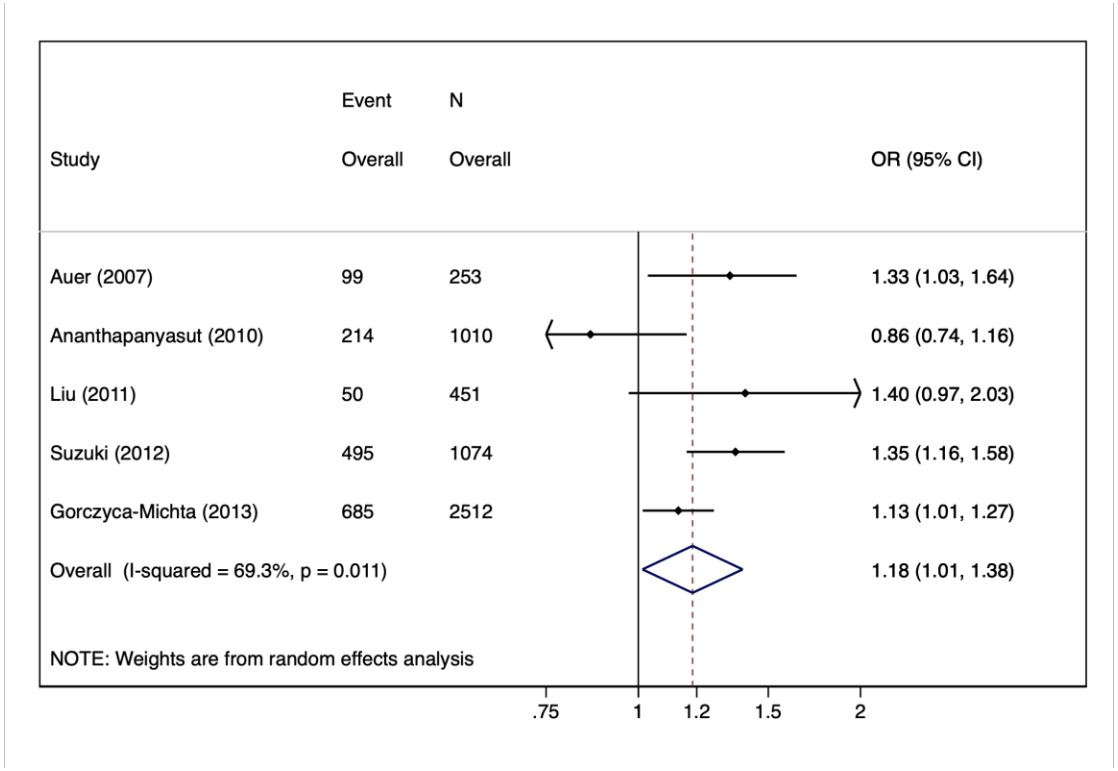


The diamonds and their widths represent ORs and 95% confidence intervals, respectively. The cutoffs (in ml/min/1.73m^2) for reduced and referent eGFR groups are: Iguchi (2008) <62.6 vs. >75.5, McManus (2009) <66 vs. >85, Deo (2010) <60 vs. ≥60, Baber (2011) <30 vs. ≥60 & ACR <30, Suzuki (2012) <60.07 vs. >73.67, Ohyama (2013) <60 vs. ≥90, Limite (2016) <60 vs. ≥90, Yonezawa (2018) <60 vs. ≥90.

Table A-12. Summary of cross-sectional study results on the association between continuous eGFR and atrial fibrillation

Study	Year	eGFR scale (ml/min/1.73m^2)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted variables
Auer	2007	Per -10	Not reported	1.21 (1.02-1.39)	Age, weight, sex, surgery for valvular heart disease, number of bypass grafts, use of arterial conduit, beta-blocker, preoperative heart rate, smoking, serum potassium
Ananthapanyasut	2010	Per 1	1.01 (1.00-1.02)	1.01 (0.99-1.02)	Age, age ≥65 years, race, systolic blood pressure, heart failure, left atrial diameter
Liu	2011	Per 1	Not reported	0.978 (0.954-1.002)	Age, hypertension duration, creatinine, interventricular septum thickness, left ventricular posterior wall thickness
Suzuki	2012	Per 1	0.98 (0.97-0.99)	0.98 (0.97-0.99)	Age, heart failure, organic cardiac disease, valvular heart disease, cardiomyopathy, diabetes, dyslipidemia, cerebral infarction or transient ischemic attack, antiarrhythmic drug class 1 and 4, digitalis, proteinuria
Gorczyca-Michta	2013	Per 1	Not reported	0.9275 (0.7073-1.2163)	Hypothyroidism, ischemic heart disease, hyperthyroidism, euthyroid goiter, myocardial infarction, heart failure, hyperlipidemia, age, left ventricular ejection fraction, hemoglobin, triglycerides, low-density lipoprotein, total cholesterol, diabetes

Figure A-2. Odds ratios (ORs) of atrial fibrillation per -15 ml/min/1.73m^2 of eGFR from cross-sectional studies



The diamonds and their widths represent ORs and 95% confidence intervals, respectively. ORs are rescaled for all studies.

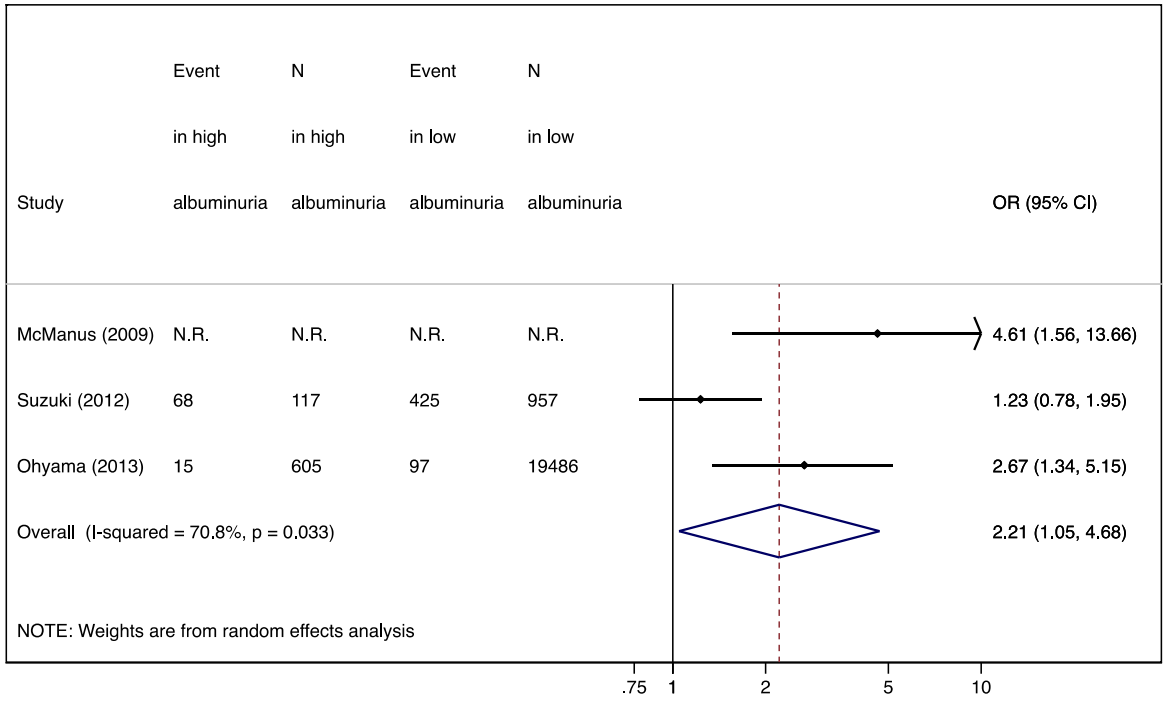
Table A-13. List of covariates adjusted for in prospective studies examining the association between albuminuria groups and atrial fibrillation

Study	Year	Adjusted variables
Alonso	2011	Age, sex, race, study site, education, income, height, smoking, drinking, diabetes, systolic blood pressure, antihypertensive medication, body mass index, high sensitivity C-reactive protein, prevalent coronary heart disease, prevalent heart failure, incident heart failure or myocardial infarction during follow-up, any hospitalization before end of follow-up
Hsu	2013	Age, sex, race, CD4 cell count, HIV RNA viral load, hypertension, diabetes, coronary artery disease, congestive heart failure, chronic lung disease, smoking, alcoholism, hyperthyroidism, hypothyroidism, body mass index, proteinuria
Lim	2017	Age, sex, body mass index, smoking, alcohol consumption, exercise frequency, diabetes, hypertension, dyslipidemia, ischemic heart disease, heart failure, stroke, chronic obstructive pulmonary disease
Bansal: JHS	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic and diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Bansal: MESA	2017	Age, age squared, sex, education, height, weight, smoking, diabetes, heart failure, myocardial infarction, stroke, systolic and diastolic blood pressure, antihypertension medication, left ventricular mass, left ventricular ejection fraction, PR duration
Molnar	2017	Age, sex, income, index year, diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, myocardial infarction, stroke/ transient ischemic attack, hemorrhage, heart failure, peripheral vascular disease, coronary artery bypass graft

Table A-14. Summary of cross-sectional study results on the association between albuminuria groups and atrial fibrillation

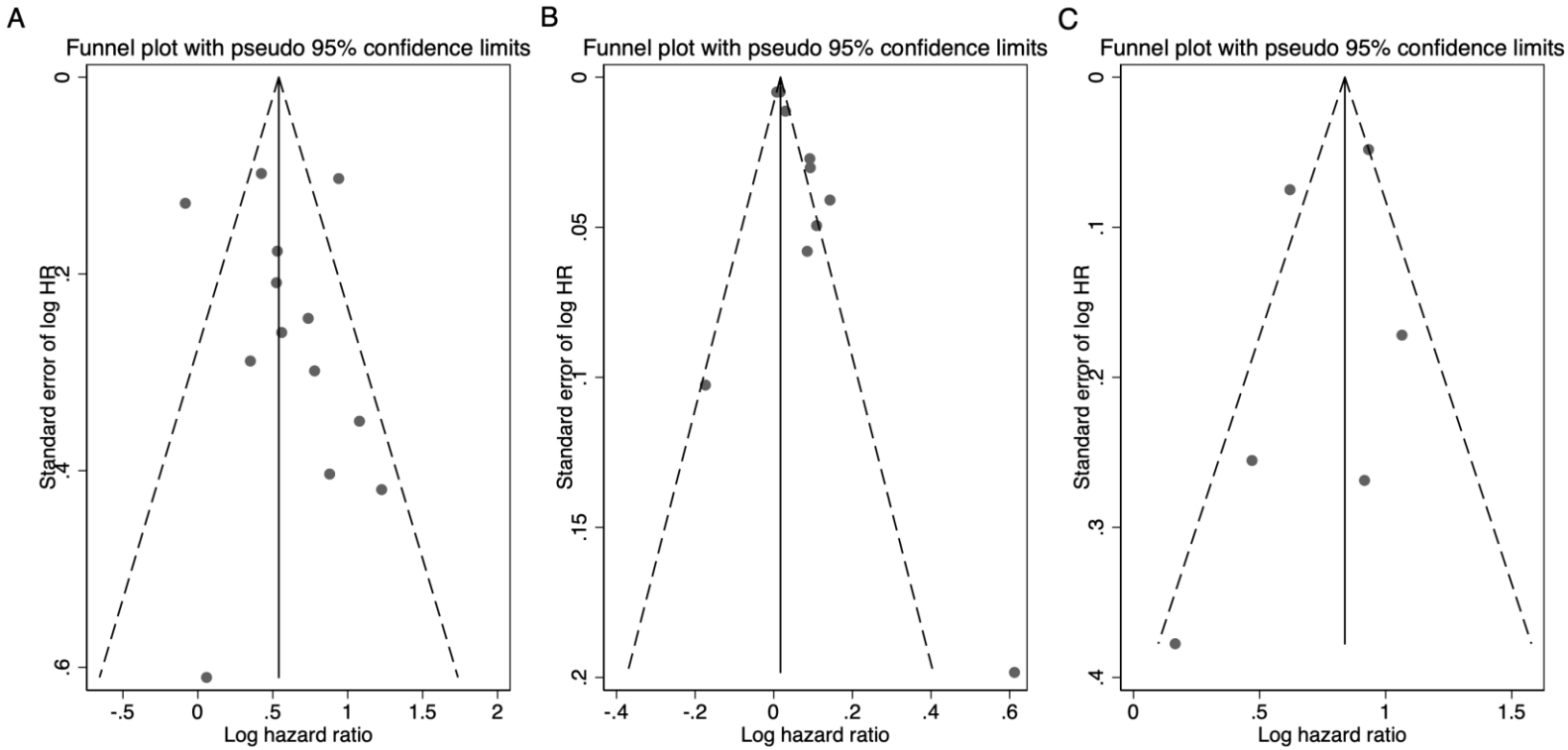
Study	Year	Proteinuria categories	Referent group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted variables
McManus	2009	ACR (mg/g): <7, 7-15, >15	ACR (mg/g): <7	7-15: 2.27 (0.78-6.63), >15: 3.88 (1.42-10.61)	7-15: 2.55 (0.83-7.83), >15: 4.61 (1.56-13.66)	Age, Age^2, gender, race, body mass index, systolic and diastolic blood pressure, hypertension, left ventricular ejection fraction, eGFR
Suzuki	2012	Urine protein: Negative, ≥1+	Urine protein: Negative	1.73 (1.17-2.56)	1.23 (0.78-1.95)	Age, heart failure, organic cardiac disease, valvular heart disease, cardiomyopathy, diabetes, dyslipidemia, cerebral infarction or TIA, antiarrhythmic drug class 1 and 4, digitalis, eGFR
Ohyama	2013	Dipstick protein: Negative, ≥1+	Dipstick protein: Negative	Not reported	2.67 (1.34-5.15)	Age, gender, hypertension, diabetes, smoking, cardiac disease, eGFR

Figure A-3. Odds ratios (ORs) of atrial fibrillation comparing high to low albuminuria groups from cross-sectional studies



The diamonds and their widths represent ORs and 95% confidence intervals, respectively. The cutoff values for high and low albuminuria groups are: McManus (2009): ACR >15 vs. <7 mg/g; Suzuki (2012): Proteinuria positive vs. negative; Ohyama (2013): Proteinuria positive vs. negative.

Figure A-4. Funnel plots of prospective studies examining the associations of eGFR and albuminuria with atrial fibrillation



(A) Includes prospective studies examining the association of reduced vs. referent eGFR groups with atrial fibrillation; (B) Includes prospective studies examining the association of continuous eGFR (per -15 ml/min/1.73m^2) with atrial fibrillation; (C) Includes prospective studies examining the association of high vs. low albuminuria groups with atrial fibrillation

Table A-15. List of covariates adjusted for in prospective studies examining the association between eGFR groups and ICD shock

Study	Year	Adjusted variables
Takahashi	2009	ICD for secondary prevention, beta-blocker, QTs interval >120ms, left ventricular ejection fraction <35%, >10 VPBs/h
Hage	2011	Age, gender, hypertension, atrial fibrillation, myocardial infarction, left ventricular ejection fraction, left bundle branch block, biventricular pacing, antiarrhythmic medications
Babu	2016	Age, gender, left ventricular ejection fraction, heart failure etiology (ischemic vs. non-ischemic), angiotensin-converting-enzyme inhibitors, beta blockers, amiodarone
Hai	2017	Age, hypertension, coronary artery disease, early ventricular tachycardia, left ventricular ejection fraction ≤35%, triple-vessel disease, successful revascularization

Table A-16. Summary of results on the associations of chronic kidney disease measures with various arrhythmias from prospective, cross-sectional, and case-control studies

Study design	Study	Year	Arrhythmia	CKD measure	Referent group	Unadjusted estimate (HR or OR)	Adjusted estimate (HR or OR)	Adjusted variables
Prospective	**Tachycardia**							
	Hreybe	2006	ICD shock for VF or VT	Serum creatinine (mg/dl): <1, 1-1.4, >1.4	<1	Not reported	HR (no 95% CI): 1-1.4: Not reported >1.4: 6.00	Age, sex, left ventricular ejection fraction, indication for ICD, beta-blockers
	Khurshid	2018	Supraventricular arrhythmias	CKD based on diagnosis codes	No CKD	Not reported	HR (95% CI): 2.43 (1.56-3.79)	Age, sex, body mass index, tobacco use, alcohol use, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, depression, venous thromboembolism, peripheral artery disease, stroke, coronary artery disease, heart failure
	Khurshid	2018	Ventricular arrhythmias	CKD based on diagnosis codes	No CKD	Not reported	HR (95% CI): 2.46 (1.80-3.37)	Age, sex, body mass index, tobacco use, alcohol use, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, depression, venous thromboembolism, peripheral artery disease, stroke, coronary artery disease, heart failure
	Kreuz	2010	ICD therapy for malignant ventricular arrhythmias	Serum creatinine (mg/dl): 1, 2	1	Not reported	OR (95% CI): 2: 3.96 (1.2-13.04)	Baseline NYHA class
	Kreuz	2011	ICD therapy for malignant	Serum creatinine (mg/dl): 1,	1	Not reported	OR (95% CI): 2: 3.7 (1.53-8.73)	Gender, statin

			ventricular arrhythmias	2				
	Robin	2006	ICD shock for VF	ESRD	No ESRD	HR (95% CI): 2.3 (1.17-4.54)	HR (95% CI): 2.67 (1.38-5.17)	Ejection fraction, ICD implant indication
	Bradycardia							
	Khurshid	2018	Bradyarrhythmias	CKD based on diagnosis codes	No CKD	Not reported	HR (95% CI): 1.37 (0.98-1.91)	Age, sex, body mass index, tobacco use, alcohol use, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, depression, venous thromboembolism, peripheral artery disease, stroke, coronary artery disease, heart failure
	Khurshid	2018	Conduction system diseases	CKD based on diagnosis codes	No CKD	Not reported	HR (95% CI): 1.87 (1.44-2.42)	Age, sex, body mass index, tobacco use, alcohol use, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, hyperthyroidism, hypothyroidism, depression, venous thromboembolism, peripheral artery disease, stroke, coronary artery disease, heart failure
	Jensen	2014	Sick sinus syndrome	eGFR ($ml/min/1.73m^2$): ≥60, <60	≥60	Not reported	HR (95% CI): 1.14 (0.63-2.17)	Age, sex, race, study clinic, hypertension, diabetes, body mass index, current smoking, low-density lipoprotein, history of cardiovascular event
Cross-sectional	**Tachycardia**							
	Soman	2002	Accelerated idioventricular rhythm	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1,	>81.5	OR (95% CI): 63.1-81.5: 1.28 (0.97-1.70), 46.2-≤63.1: 1.53 (1.17-2), ≤46.2: 1.39 (1.06-1.83), Dialysis: 1.91 (1.3-2.8)	OR (95% CI): 63.1-81.5: 1.31 (0.96-1.8), 46.2-≤63.1: 1.55 (1.10-2.17), ≤46.2: 1.56 (1.07-2.28),	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme

				≤46.2, Dialysis			Dialysis: 2.43 (1.40-4.20)	inhibitor, diabetes, hemoglobin
	Soman	2002	Nonsustained ventricular tachycardia	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1, ≤46.2, Dialysis	>81.5	OR (95% CI): 63.1-81.5: 1.30 (0.93-1.82), 46.2-≤63.1: 1.75 (1.27-2.40), ≤46.2: 1.45 (1.05-2.02), Dialysis: 1.04 (0.59-1.84)	OR (95% CI): 63.1-81.5: 1.41 (1-1.2), 46.2-≤63.1: 1.7 (1.14-2.53), ≤46.2: 1.39 (0.89-2.18), Dialysis: 1.24 (0.6-2.6)	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, diabetes, hemoglobin
	Soman	2002	Sustained ventricular tachycardia	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1, ≤46.2, Dialysis	>81.5	OR (95% CI): 63.1-81.5: 1.43 (0.99-2.05), 46.2-≤63.1: 1.69 (1.19-2.41), ≤46.2: 1.82 (1.28-2.57), Dialysis: 1.7 (1.01-2.88)	OR (95% CI): 63.1-81.5: 1.66 (1.10-2.5), 46.2-≤63.1: 2 (1.29-3.13), ≤46.2: 2.19 (1.36-3.5), Dialysis: 2.07 (1.02-4.22)	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, diabetes, hemoglobin
	Soman	2002	Ventricular fibrillation	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1, ≤46.2, Dialysis	>81.5	OR (95% CI): 63.1-81.5: 1.55 (1.09-2.20), 46.2-≤63.1: 1.59 (1.12-2.25), ≤46.2: 1.99 (1.42-2.78), Dialysis: 1.47 (0.85-2.52)	OR (95% CI): 63.1-81.5: 1.63 (1.08-2.47), 46.2-≤63.1: 1.91 (1.22-2.98), ≤46.2: 2.05 (1.29-3.26), Dialysis: 2.42 (1.13-5.15)	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, diabetes, hemoglobin
	Bradycardia							
	Soman	2002	Complete heart block	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1, ≤46.2, Dialysis	>81.5	OR (95% CI): 63.1-81.5: 1.79 (1.18-2.72), 46.2-≤63.1: 2.27 (1.52-3.4), ≤46.2: 2.94 (1.99-4.35), Dialysis: 3.56 (2.14-5.9)	OR (95% CI): 63.1-81.5: 1.73 (1.08-2.77), 46.2-≤63.1: 2.73 (1.68-4.43), ≤46.2: 2.82 (1.71-4.65), Dialysis: 3.64 (1.77-7.48)	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, diabetes, hemoglobin
	Soman	2002	Asystole	Corrected CrCl (ml/min/72kg): >81.5, 63.1-81.5, 46.2-≤63.1, ≤46.2, Dialysis	>81.5	OR (95% CI): 63.1-81.5: 1.65 (1.07-2.56), 46.2-≤63.1: 1.65 (1.07-2.56), ≤46.2: 3.13 (2.10-4.65), Dialysis: 1.84 (0.98-3.46)	OR (95% CI): 63.1-81.5: 1.75 (1.08-2.83), 46.2-≤63.1: 1.57 (0.92-2.66), ≤46.2: 2.8 (1.69-4.63), Dialysis: 2.3 (1.00-5.57)	Age, gender, race, admission diagnosis, heart failure, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor, diabetes, hemoglobin
Case-control	**Tachycardia**							
	Dalal	2012	Ventricular fibrillation (resuscitated after myocardial infarction)	eGFR (ml/min/1.73m^2): 115-190, 101-115, 90-101,	101-115	OR (95% CI): 115-190: 0.9 (0.5-1.6), 90-101: 1.2 (0.7-2), 79-90: 1.9 (1.1-3.1), 29-79: 4.3 (2.7-7.1)	OR (95% CI): 115-190: 1 (0.5-1.9), 90-101: 1.5 (0.8-2.9), 79-90: 2.8 (1.5-5.3), 29-79: 6.7 (3.6-12.4)	Age, gender, body mass index, smoking hypertension, hypercholesterolemia, diabetes, family history

				79-90, 29-79				of sudden cardiac death, diuretic angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker, statin, sodium, potassium, hemoglobin
	Mene-Afejuku	2017	Premature ventricular contraction	Creatinine: Per 1 unit (umol/L)	Creatinine: Per 1 unit (umol/L)	Not reported	No statistically significant association (detail could not be found)	Urea, left ventricular ejection fraction, systolic blood pressure
	Mene-Afejuku	2017	Ventricular tachycardia	Creatinine: Per 1 unit (umol/L)	Creatinine: Per 1 unit (umol/L)	Not reported	Statistically significant association (detail could not be found)	Urea, systolic blood pressure, premature ventricular contraction
	Bradycardia							
	Lu (presence of beta-blocker)	2016	Symptomatic bradycardia	eGFR: Per 1 unit (ml/min/1.73m^2)	eGFR: Per 1 unit	OR (95% CI): 0.97 (0.96-0.98)	OR (95% CI): 0.98 (0.96-1.00)	Age, sex, hypertension, diabetes, body mass index, Malay vs non-Malay, concomitant use of rate-controlling drugs, sodium, potassium
	Lu (absence of beta-blocker)	2016	Symptomatic bradycardia	eGFR: Per 1 unit (ml/min/1.73m^2)	eGFR: Per 1 unit	OR (95% CI): 0.99 (0.97-0.99)	OR (95% CI): 0.99 (0.97-1.01)	Age, sex, hypertension, diabetes, body mass index, Malay vs non-Malay, concomitant use of rate-controlling drugs, sodium, potassium

Appendix B: Supplementary materials for Chapter 2

Figure B-1. Study flow diagram

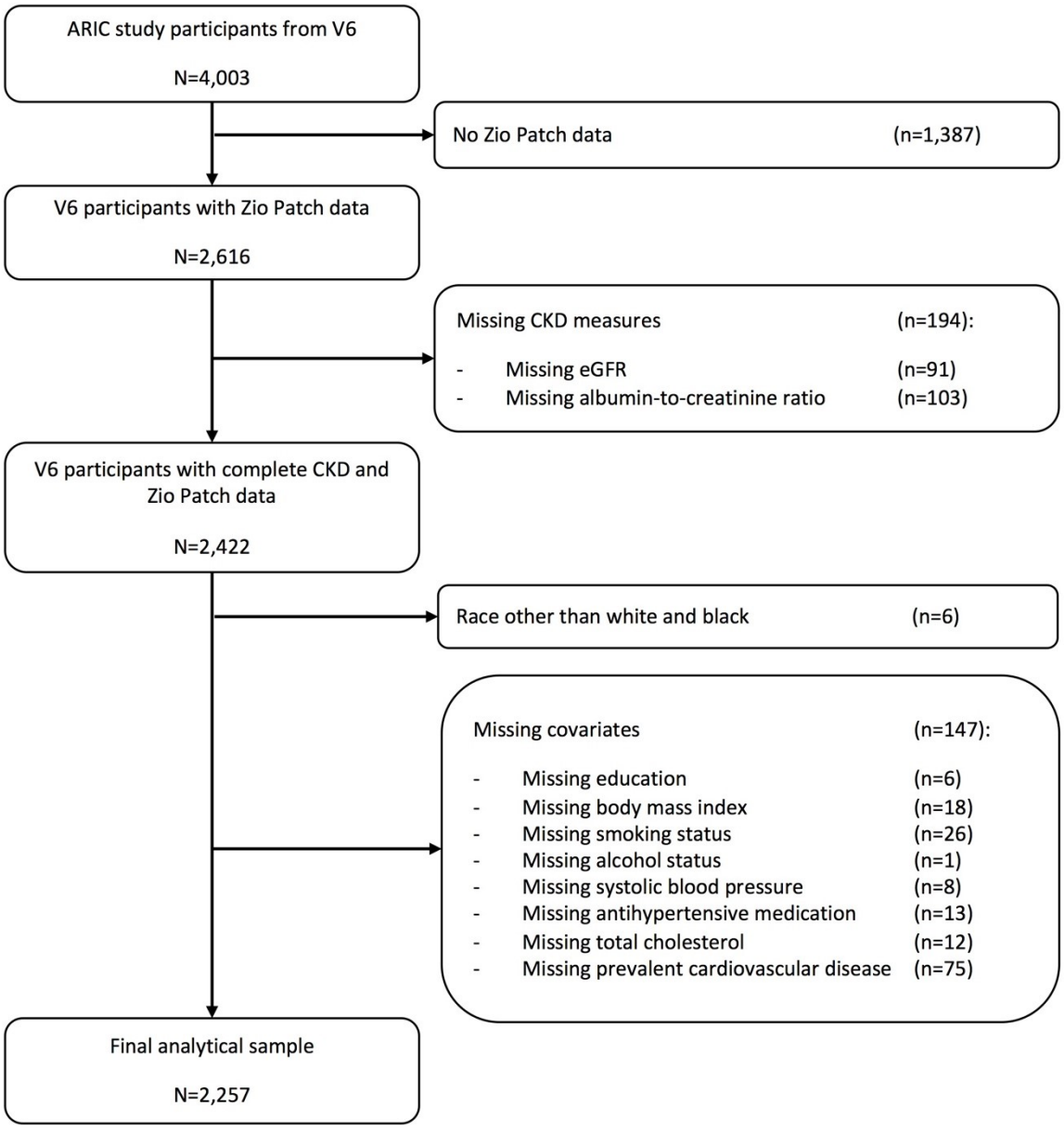
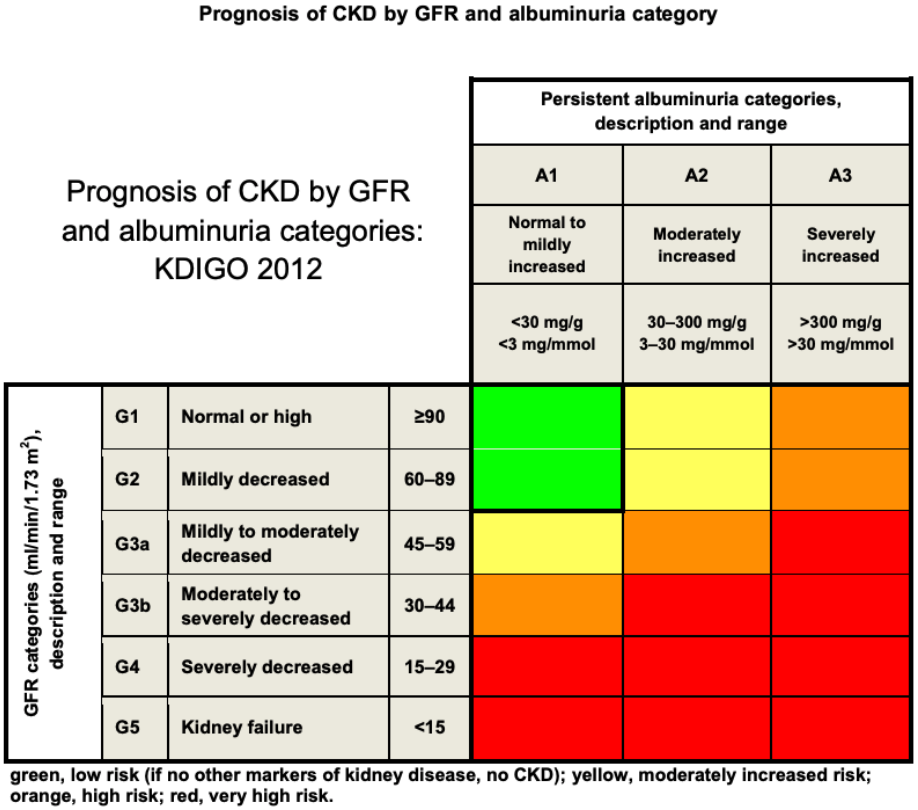


Figure B-2. Categorization of glomerular filtration rate (GFR) and albuminuria according to KDIGO*



*The figure is from the 2017 KDIGO Clinical Practice Guideline:

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.

Table B-1. List of drugs commonly associated with QT-prolongation and torsades de pointes

Antiarrhythmic	Antimicrobial	Antidepressant	Antipsychotic	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Setraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

*Accessed from https://www.uspharmacist.com/article/drug-induced-qt-prolongation

Table B-2. Associations of chronic kidney disease (CKD) status with prevalence of major arrhythmias

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
			PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P
Atrial fibrillation	Model 1	ref	1.54 (1.05, 2.26)	0.03	2.02 (1.34, 3.06)	0.001	2.65 (1.72, 4.09)	<0.001
	Model 2	ref	1.45 (0.98, 2.14)	0.07	1.78 (1.15, 2.73)	0.01	2.22 (1.42, 3.49)	0.001
	Model 3	ref	1.29 (0.87, 1.89)	0.20	1.44 (0.91, 2.28)	0.12	1.91 (1.21, 3.01)	0.01
Non-sustained ventricular tachycardia	Model 1	ref	1.17 (1.00, 1.37)	0.05	1.46 (1.23, 1.73)	<0.001	1.50 (1.24, 1.82)	<0.001
	Model 2	ref	1.13 (0.97, 1.32)	0.12	1.35 (1.14, 1.60)	0.001	1.34 (1.09, 1.63)	0.004
	Model 3	ref	1.07 (0.91, 1.25)	0.43	1.20 (1.01, 1.44)	0.04	1.14 (0.93, 1.41)	0.21
Long pause	Model 1	ref	1.91 (1.01, 3.62)	0.05	1.56 (0.72, 3.41)	0.26	3.52 (1.74, 7.12)	<0.001
	Model 2	ref	1.65 (0.88, 3.13)	0.12	1.17 (0.51, 2.69)	0.71	2.39 (1.10, 5.20)	0.03
	Model 3	ref	1.49 (0.77, 2.87)	0.23	0.92 (0.39, 2.17)	0.85	1.91 (0.82, 4.49)	0.14
Atrioventricular block	Model 1	ref	0.95 (0.47, 1.92)	0.89	0.53 (0.18, 1.54)	0.24	1.06 (0.40, 2.81)	0.91
	Model 2	ref	0.92 (0.47, 1.83)	0.82	0.49 (0.17, 1.46)	0.20	0.95 (0.34, 2.65)	0.92
	Model 3	ref	0.72 (0.36, 1.46)	0.36	0.36 (0.12, 1.07)	0.07	0.60 (0.22, 1.66)	0.33

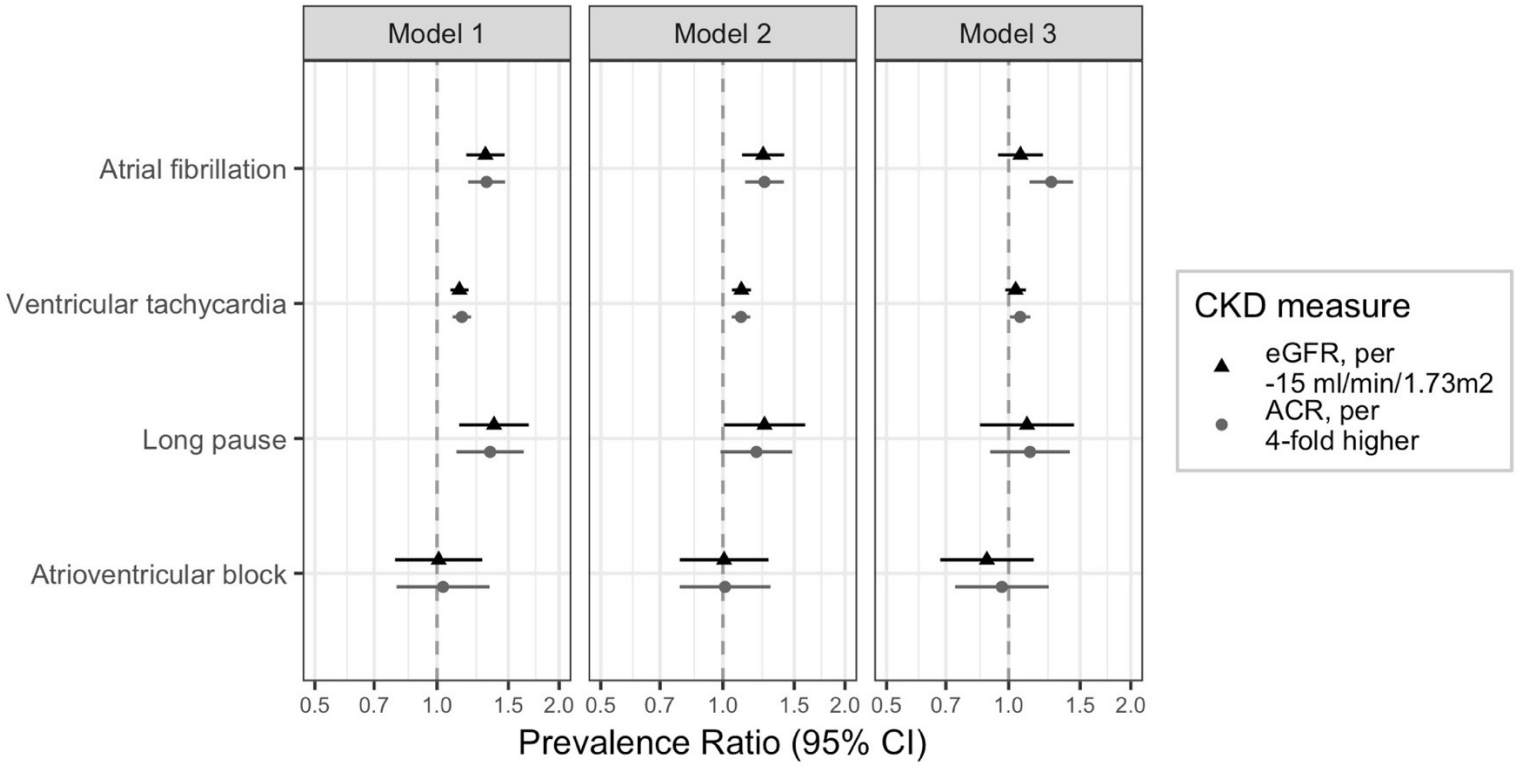
PR=prevalence ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, medication, QT-prolonging drug

Figure B-2. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with prevalence of major arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR

Table B-3. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with prevalence of major arrhythmias

		eGFR, per -15 ml/min/1.73m^2		ACR, per 4-fold increase	
		PR (95% CI)	**P**	**PR (95% CI)**	**P**
Atrial fibrillation	Model 1	1.32 (1.18, 1.47)	<0.001	1.32 (1.19, 1.47)	<0.001
	Model 2	1.26 (1.12, 1.42)	<0.001	1.27 (1.13, 1.41)	<0.001
	Model 3	1.07 (0.94, 1.21)	0.30	1.27 (1.13, 1.44)	<0.001
Non-sustained ventricular tachycardia	Model 1	1.14 (1.08, 1.20)	<0.001	1.15 (1.09, 1.21)	<0.001
	Model 2	1.11 (1.05, 1.17)	<0.001	1.11 (1.05, 1.17)	<0.001
	Model 3	1.04 (0.98, 1.10)	0.19	1.07 (1.01, 1.13)	0.03
Long pause	Model 1	1.38 (1.13, 1.68)	0.001	1.35 (1.12, 1.64)	0.002
	Model 2	1.27 (1.01, 1.60)	0.05	1.21 (0.99, 1.48)	0.07
	Model 3	1.11 (0.85, 1.45)	0.45	1.13 (0.90, 1.42)	0.30
Atrioventricular block	Model 1	1.01 (0.79, 1.29)	0.94	1.03 (0.79, 1.35)	0.80
	Model 2	1.01 (0.78, 1.30)	0.96	1.01 (0.78, 1.31)	0.92
	Model 3	0.88 (0.68, 1.15)	0.36	0.96 (0.74, 1.25)	0.78

PR=prevalence ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, medication, QT-prolonging drug, eGFR or ACR

Table B-4. Associations of chronic kidney disease (CKD) status with percent time in atrial fibrillation and frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
Percent time			**Difference in percent time (95% CI), %**	**P**	**Difference in percent time (95% CI), %**	**P**	**Difference in percent time (95% CI), %**	**P**
Atrial fibrillation	Model 1	ref	0.03 (0.01, 0.05)	0.01	0.05 (0.03, 0.08)	<0.001	0.08 (0.05, 0.11)	<0.001
	Model 2	ref	0.02 (0.00, 0.04)	0.05	0.05 (0.02, 0.07)	0.001	0.07 (0.04, 0.10)	<0.001
	Model 3	ref	0.02 (-0.01, 0.04)	0.14	0.03 (0.01, 0.06)	0.01	0.06 (0.03, 0.09)	<0.001
Frequency			**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Non-sustained ventricular tachycardia	Model 1	ref	0.37 (0.11, 1.22)	0.10	1.82 (0.37, 8.96)	0.46	0.67 (0.20, 2.23)	0.52
	Model 2	ref	0.39 (0.13, 1.16)	0.09	1.87 (0.48, 7.37)	0.37	0.69 (0.22, 2.17)	0.53
	Model 3	ref	0.36 (0.10, 1.30)	0.12	1.73 (0.43, 7.02)	0.44	0.52 (0.12, 2.21)	0.37
Long pause	Model 1	ref	9.86 (2.92, 33.34)	<0.001	4.06 (1.01, 16.31)	0.05	27.81 (5.89, 131.24)	<0.001
	Model 2	ref	12.12 (3.50, 41.95)	<0.001	6.22 (1.29, 29.97)	0.02	34.09 (4.89, 237.60)	<0.001
	Model 3	ref	8.72 (2.25, 33.78)	0.002	3.30 (0.61, 17.96)	0.17	17.73 (3.91, 80.37)	<0.001
Atrioventricular block	Model 1	ref	0.15 (0.02, 1.12)	0.07	0.07 (0.01, 0.43)	0.004	0.02 (0.00, 0.10)	<0.001
	Model 2	ref	57.50 (3.74, 884.55)	0.004	0.03 (0.01, 0.05)	<0.001	0.01 (0.00, 0.11)	<0.001
	Model 3	ref	0.08 (0.01, 0.65)	0.02	0.00 (0.00, 0.04)	<0.001	0.01 (0.00, 0.14)	<0.001

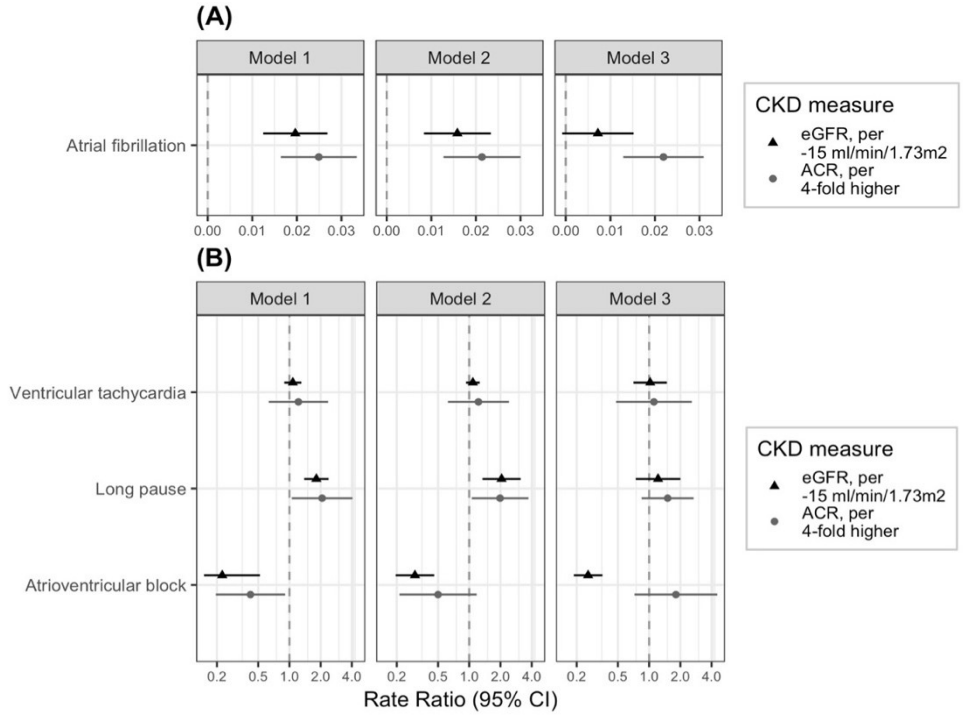
RR=rate ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

Figure B-3. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with (A) percent time in atrial fibrillation and (B) frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block



(A) Association of eGFR or ACR with percent time in atrial fibrillation; (B) Association of eGFR or ACR with frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block
Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR

Table B-5. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with percent time in atrial fibrillation and frequency of non-sustained ventricular tachycardia, long pause, and atrioventricular block

		eGFR, per -15 ml/min/1.73m^2		ACR, per 4-fold increase	
Percent time		**Difference in percent time (95% CI), %**	**P**	**Difference in percent time (95% CI), %**	**P**
Atrial fibrillation	Model 1	0.02 (0.01, 0.03)	<0.001	0.02 (0.02, 0.03)	<0.001
	Model 2	0.02 (0.01, 0.02)	<0.001	0.02 (0.01, 0.03)	<0.001
	Model 3	0.01 (-0.00, 0.02)	0.08	0.02 (0.01, 0.03)	<0.001
Frequency		**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Non-sustained ventricular tachycardia	Model 1	1.08 (0.89, 1.31)	0.44	1.22 (0.63, 2.36)	0.55
	Model 2	1.08 (0.93, 1.26)	0.31	1.23 (0.62, 2.41)	0.56
	Model 3	1.02 (0.71, 1.48)	0.90	1.11 (0.48, 2.58)	0.80
Long pause	Model 1	1.82 (1.38, 2.39)	<0.001	2.07 (1.05, 4.06)	0.04
	Model 2	2.05 (1.34, 3.13)	0.001	1.98 (1.06, 3.72)	0.03
	Model 3	1.22 (0.74, 2.00)	0.43	1.51 (0.85, 2.69)	0.16
Atrioventricular block	Model 1	0.22 (0.10, 0.52)	<0.001	0.42 (0.19, 0.91)	0.03
	Model 2	0.30 (0.20, 0.46)	<0.001	0.50 (0.21, 1.18)	0.11
	Model 3	0.26 (0.19, 0.35)	<0.001	1.81 (0.72, 4.55)	0.21

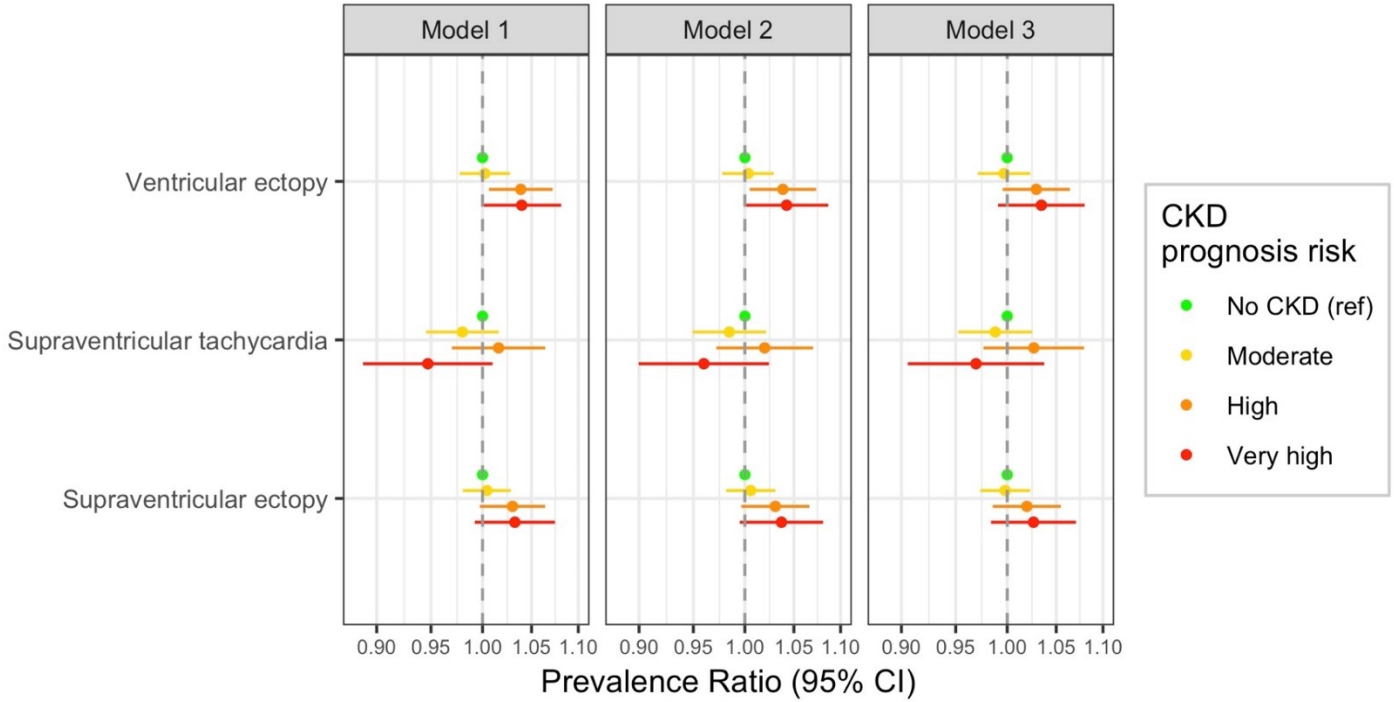
RR=rate ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR

Figure B-4. Associations of chronic kidney disease (CKD) status with prevalence of minor arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug
*Supraventricular tachycardia and ectopy were examined among participants who do not have chronic atrial fibrillation

Table B-6. Associations of chronic kidney disease (CKD) status with prevalence of minor arrhythmias

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
			PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P
Ventricular ectopy	Model 1	ref	1.00 (0.98, 1.03)	0.86	1.04 (1.01, 1.07)	0.02	1.04 (1.00, 1.08)	0.05
	Model 2	ref	1.00 (0.98, 1.03)	0.81	1.04 (1.00, 1.07)	0.03	1.04 (1.00, 1.09)	0.05
	Model 3	ref	1.00 (0.97, 1.02)	0.82	1.03 (1.00, 1.06)	0.09	1.03 (0.99, 1.08)	0.12
Supraventricular tachycardia[§]	Model 1	ref	0.98 (0.95, 1.02)	0.28	1.02 (0.97, 1.06)	0.50	0.95 (0.89, 1.01)	0.10
	Model 2	ref	0.98 (0.95, 1.02)	0.41	1.02 (0.97, 1.07)	0.42	0.96 (0.90, 1.02)	0.22
	Model 3	ref	0.99 (0.95, 1.03)	0.53	1.03 (0.98, 1.08)	0.30	0.97 (0.91, 1.04)	0.37
Supraventricular ectopy[§]	Model 1	ref	1.00 (0.98, 1.03)	0.73	1.03 (1.00, 1.06)	0.07	1.03 (0.99, 1.07)	0.11
	Model 2	ref	1.01 (0.98, 1.03)	0.64	1.03 (1.00, 1.07)	0.08	1.04 (0.99, 1.08)	0.09
	Model 3	ref	1.00 (0.97, 1.02)	0.88	1.02 (0.99, 1.05)	0.26	1.03 (0.98, 1.07)	0.23

PR=prevalence ratio; CI=confidence interval

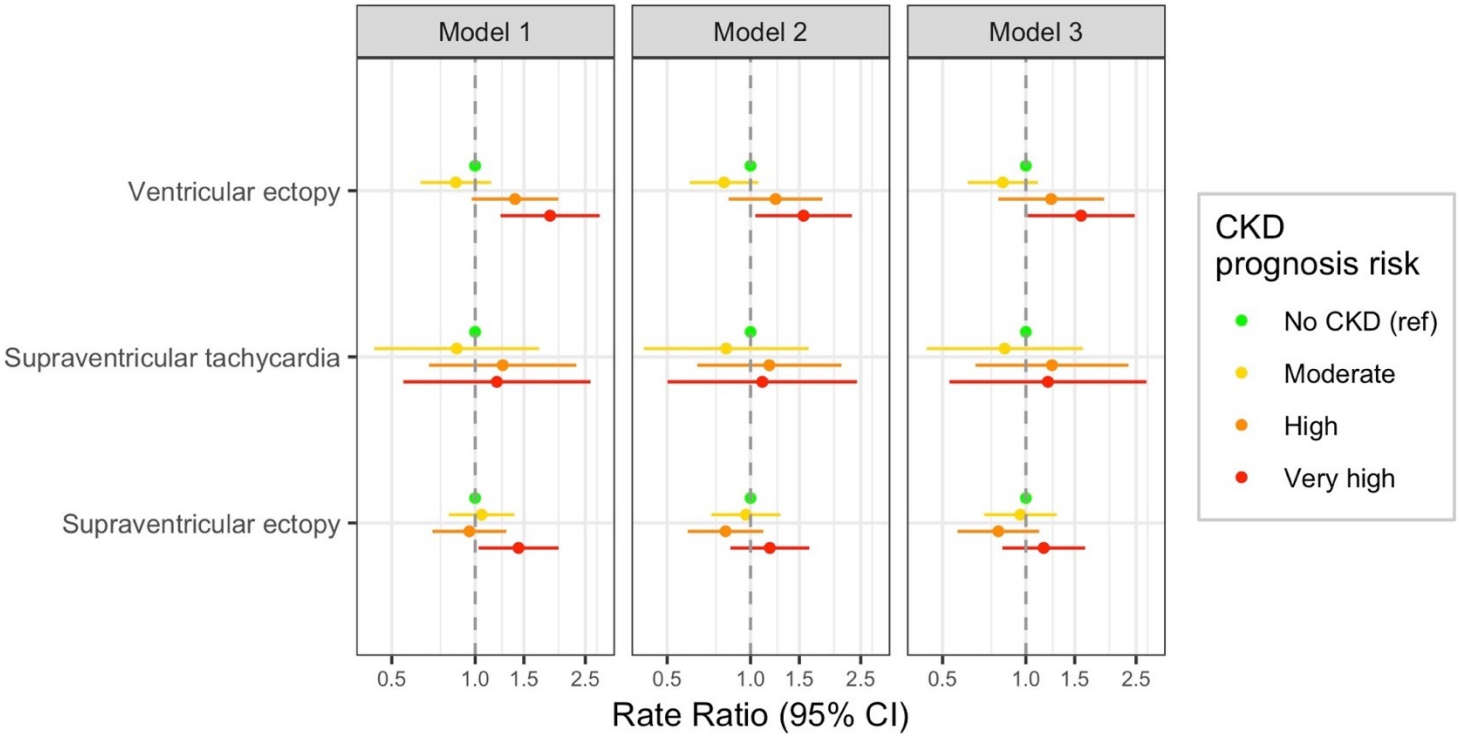
Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, medication, QT-prolonging drug

[§]Among participants who do not have chronic atrial fibrillation

Figure B-5. Associations of chronic kidney disease (CKD) status with frequency of minor arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug
* Supraventricular tachycardia and ectopy were examined among participants who do not have chronic atrial fibrillation

Table B-7. Associations of chronic kidney disease (CKD) status with frequency of minor arrhythmias

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
Frequency of arrhythmia episodes			**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Ventricular ectopy	Model 1	ref	0.85 (0.63, 1.14)	0.28	1.39 (0.97, 2.00)	0.07	1.86 (1.23, 2.82)	0.003
	Model 2	ref	0.80 (0.60, 1.07)	0.13	1.23 (0.83, 1.82)	0.30	1.55 (1.04, 2.32)	0.03
	Model 3	ref	0.82 (0.62, 1.10)	0.20	1.23 (0.79, 1.92)	0.35	1.58 (1.01, 2.47)	0.04
Supraventricular tachycardia[§]	Model 1	ref	0.86 (0.43, 1.70)	0.66	1.26 (0.68, 2.32)	0.46	1.20 (0.55, 2.61)	0.65
	Model 2	ref	0.82 (0.41, 1.62)	0.56	1.17 (0.64, 2.13)	0.61	1.10 (0.50, 2.43)	0.81
	Model 3	ref	0.84 (0.44, 1.61)	0.60	1.24 (0.66, 2.35)	0.50	1.20 (0.53, 2.73)	0.66
Supraventricular ectopy[§]	Model 1	ref	1.05 (0.80, 1.39)	0.70	0.95 (0.70, 1.30)	0.76	1.43 (1.03, 2.00)	0.03
	Model 2	ref	0.96 (0.72, 1.28)	0.79	0.81 (0.59, 1.11)	0.20	1.17 (0.85, 1.63)	0.34
	Model 3	ref	0.96 (0.71, 1.29)	0.77	0.80 (0.57, 1.12)	0.19	1.16 (0.82, 1.63)	0.40

RR=rate ratio; CI=confidence interval

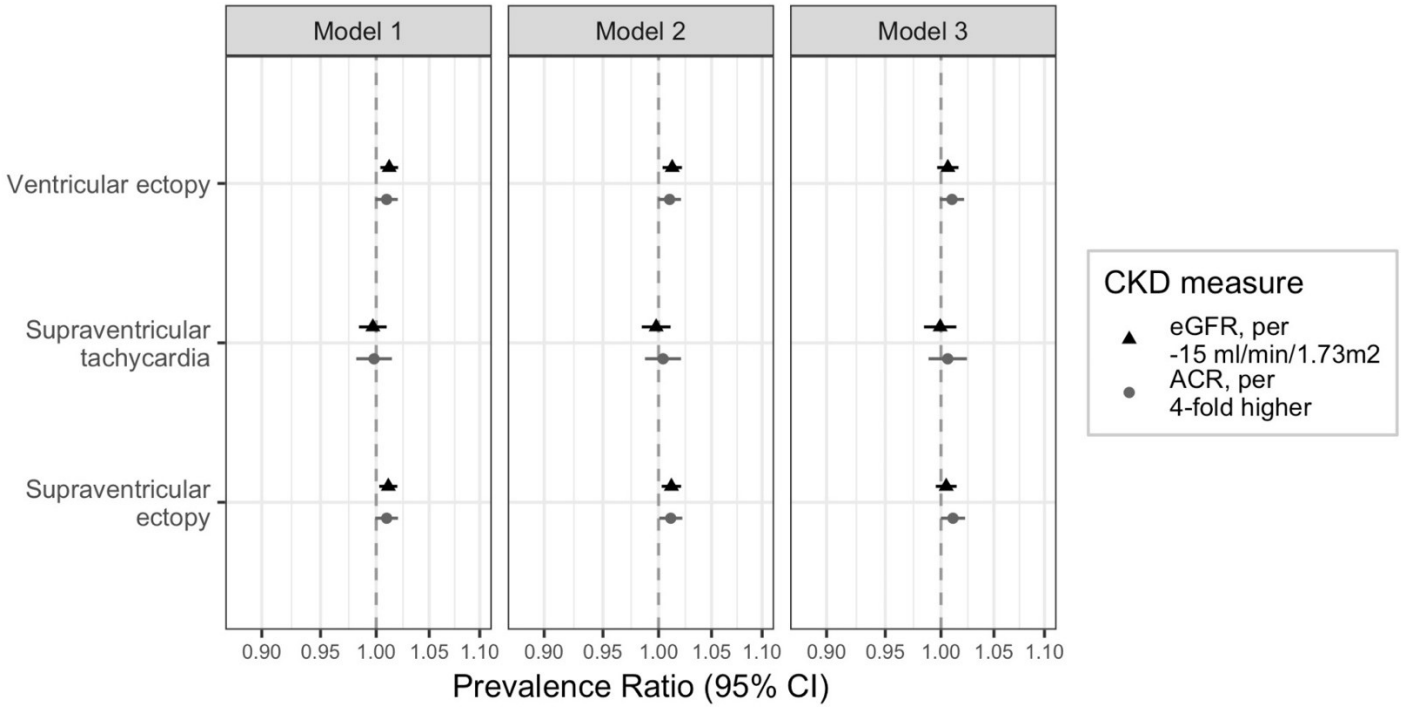
Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

[§]Among participants who do not have chronic atrial fibrillation

Figure B-6. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with prevalence of minor arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR
*Supraventricular tachycardia and ectopy were examined among participants who do not have chronic atrial fibrillation

Table B-8. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with prevalence of minor arrhythmias

		eGFR, per -15 ml/min/1.73m^2		ACR, per 4-fold increase	
		PR (95% CI)	**P**	**PR (95% CI)**	**P**
Ventricular ectopy	Model 1	1.01 (1.00, 1.02)	0.004	1.01 (1.00, 1.02)	0.07
	Model 2	1.01 (1.00, 1.02)	0.01	1.01 (1.00, 1.02)	0.06
	Model 3	1.01 (1.00, 1.02)	0.21	1.01 (1.00, 1.02)	0.07
Supraventricular tachycardia[§]	Model 1	1.00 (0.98, 1.01)	0.64	1.00 (0.98, 1.01)	0.81
	Model 2	1.00 (0.98, 1.01)	0.74	1.00 (0.99, 1.02)	0.63
	Model 3	1.00 (0.98, 1.01)	0.92	1.01 (0.99, 1.02)	0.49
Supraventricular ectopy[§]	Model 1	1.01 (1.00, 1.02)	0.01	1.01 (1.00, 1.02)	0.07
	Model 2	1.01 (1.00, 1.02)	0.01	1.01 (1.00, 1.02)	0.04
	Model 3	1.00 (1.00, 1.01)	0.33	1.01 (1.00, 1.02)	0.05

PR=prevalence ratio; CI=confidence interval

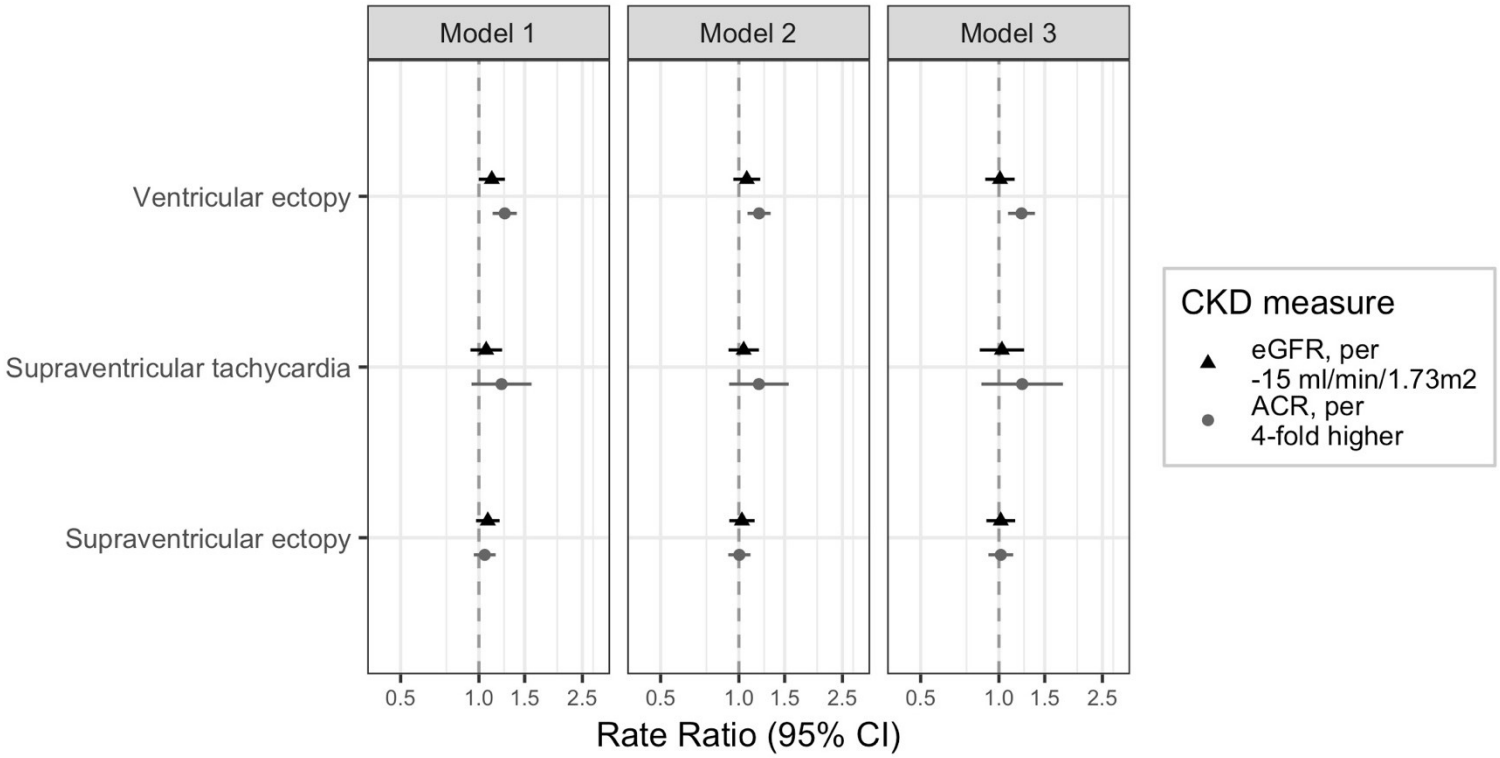
Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, medication, QT-prolonging drug, eGFR or ACR

[§]Among participants who do not have chronic atrial fibrillation

Figure B-7. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with frequency of minor arrhythmias



Model 1: Crude
Model 2: Age, sex, race, study center, education
Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR
*Supraventricular tachycardia and ectopy were examined among participants who do not have chronic atrial fibrillation

Table B-9. Associations of estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) with frequency of minor arrhythmias

		eGFR, per -15 ml/min/1.73m^2		ACR, per 4-fold increase	
Frequency of arrhythmia episodes		**RR (95% CI)**	**P**	**RR (95% CI)**	**P**
Ventricular ectopy	Model 1	1.12 (1.00, 1.26)	0.05	1.26 (1.13, 1.40)	<0.001
	Model 2	1.07 (0.95, 1.21)	0.25	1.20 (1.08, 1.32)	0.001
	Model 3	1.01 (0.89, 1.15)	0.89	1.22 (1.08, 1.38)	0.001
Supraventricular tachycardia[§]	Model 1	1.07 (0.93, 1.23)	0.37	1.22 (0.94, 1.59)	0.14
	Model 2	1.04 (0.91, 1.19)	0.54	1.19 (0.92, 1.55)	0.19
	Model 3	1.03 (0.84, 1.25)	0.79	1.23 (0.86, 1.76)	0.26
Supraventricular ectopy[§]	Model 1	1.08 (0.97, 1.20)	0.14	1.05 (0.96, 1.16)	0.30
	Model 2	1.03 (0.92, 1.15)	0.64	1.00 (0.91, 1.11)	0.94
	Model 3	1.02 (0.89, 1.16)	0.80	1.02 (0.91, 1.13)	0.76

RR=rate ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug, eGFR or ACR

[§]Among participants who do not have chronic atrial fibrillation

Table B-10. Associations of chronic kidney disease (CKD) status with prevalence of major arrhythmias using additional arrhythmia events captured from hospitalization records

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
			PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P
Atrial fibrillation	Model 1	ref	1.60 (1.12, 2.29)	0.01	2.12 (1.45, 3.11)	<0.001	2.66 (1.77, 3.98)	<0.001
	Model 2	ref	1.50 (1.05, 2.16)	0.03	1.87 (1.26, 2.78)	0.002	2.24 (1.47, 3.41)	<0.001
	Model 3	ref	1.33 (0.94, 1.89)	0.11	1.51 (0.99, 2.29)	0.05	1.90 (1.25, 2.90)	0.003
Non-sustained ventricular tachycardia	Model 1	ref	1.17 (1.00, 1.37)	0.05	1.47 (1.24, 1.74)	<0.001	1.50 (1.24, 1.82)	<0.001
	Model 2	ref	1.13 (0.97, 1.32)	0.11	1.36 (1.15, 1.61)	<0.001	1.34 (1.10, 1.63)	0.004
	Model 3	ref	1.07 (0.91, 1.25)	0.43	1.21 (1.02, 1.45)	0.03	1.14 (0.93, 1.41)	0.20
Long pause	Model 1	ref	1.88 (1.01, 3.50)	0.05	1.62 (0.77, 3.42)	0.21	3.31 (1.65, 6.63)	0.001
	Model 2	ref	1.64 (0.88, 3.05)	0.12	1.23 (0.55, 2.73)	0.61	2.28 (1.06, 4.88)	0.03
	Model 3	ref	1.51 (0.80, 2.86)	0.21	0.99 (0.43, 2.30)	0.99	1.90 (0.82, 4.43)	0.14
Atrioventricular block	Model 1	ref	0.95 (0.47, 1.92)	0.89	0.92 (0.39, 2.18)	0.85	1.06 (0.40, 2.81)	0.91
	Model 2	ref	0.91 (0.46, 1.80)	0.78	0.84 (0.36, 1.95)	0.68	0.92 (0.33, 2.56)	0.87
	Model 3	ref	0.72 (0.36, 1.46)	0.37	0.62 (0.26, 1.46)	0.27	0.61 (0.22, 1.67)	0.33

PR=prevalence ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

Table B-11. Associations of chronic kidney disease (CKD) status with prevalence of major arrhythmias after excluding participants taking antiarrhythmic medications

		No CKD	CKD with moderate risk		CKD with high risk		CKD with very high risk	
			PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P
Atrial fibrillation	Model 1	ref	1.27 (0.80, 2.03)	0.31	2.02 (1.25, 3.27)	0.00	2.75 (1.67, 4.53)	<0.001
	Model 2	ref	1.19 (0.74, 1.92)	0.46	1.81 (1.09, 3.00)	0.02	2.25 (1.35, 3.75)	0.002
	Model 3	ref	1.07 (0.66, 1.73)	0.78	1.52 (0.91, 2.55)	0.11	1.76 (1.03, 3.01)	0.04
Non-sustained ventricular tachycardia	Model 1	ref	1.19 (1.01, 1.40)	0.04	1.43 (1.20, 1.71)	0.00	1.49 (1.21, 1.82)	<0.001
	Model 2	ref	1.14 (0.97, 1.34)	0.11	1.32 (1.11, 1.58)	0.00	1.30 (1.05, 1.61)	0.02
	Model 3	ref	1.07 (0.91, 1.26)	0.42	1.19 (0.98, 1.43)	0.07	1.10 (0.88, 1.37)	0.39
Long pause	Model 1	ref	1.87 (0.92, 3.83)	0.09	1.20 (0.46, 3.13)	0.71	3.81 (1.76, 8.25)	0.001
	Model 2	ref	1.53 (0.74, 3.16)	0.25	0.88 (0.31, 2.49)	0.81	2.38 (0.97, 5.80)	0.06
	Model 3	ref	1.37 (0.64, 2.95)	0.42	0.74 (0.26, 2.10)	0.58	1.74 (0.64, 4.69)	0.28
Atrioventricular block	Model 1	ref	1.03 (0.51, 2.10)	0.93	0.43 (0.13, 1.46)	0.18	1.15 (0.43, 3.06)	0.79
	Model 2	ref	0.98 (0.49, 1.96)	0.95	0.39 (0.12, 1.32)	0.13	0.99 (0.35, 2.80)	0.99
	Model 3	ref	0.74 (0.37, 1.51)	0.41	0.28 (0.08, 0.97)	0.04	0.60 (0.22, 1.69)	0.34

PR=prevalence ratio; CI=confidence interval

Model 1: Crude

Model 2: Age, sex, race, study center, education

Model 3: Model 2 + body mass index, current smoking and alcohol, systolic blood pressure, antihypertensive drugs, diabetes, prevalent cardiovascular disease, total and HDL cholesterol, antiarrhythmic medication, QT-prolonging drug

Table B-12. Baseline characteristics comparing participants who did and did not undergo two-week continuous electrocardiogram (ECG) monitoring

Characteristics	Underwent monitoring n=2257	Did not undergo monitoring n=1063*
Age, years (SD)	79.1 (4.6)	80.2 (4.9)
Male, %	56.7	60.1
White, %	23.5	18.3
Study center, %		
Forsyth County, NC	22.8	23.1
Jackson, MS	21.9	16.5
Minneapolis, MN	29.0	35.0
Washington County, MD	26.3	25.4
Education, %		
< High school	12.0	11.4
High school graduate	41.5	40.0
College or graduate school	46.5	48.6
Body mass index, kg/m^2 (SD)	28.3 (5.3)	28.2 (5.6)
Current cigarette smoker, %	7.0	6.7
Current drinker, %	51.6	50.7
Systolic blood pressure, mmHg (SD)	134.9 (18.8)	135.5 (19.1)
Antihypertensive medication, %	76.3	77.6
Diabetes, %	33.4	32.5
Prevalent cardiovascular disease, %	23.8	27.8
Heart failure, %	12.5	16.7
Coronary heart disease, %	14.0	15.4
Stroke, %	4.4	5.2
Medication for arrhythmia, %	8.9	10.4
QT-prolonging medication, %	10.4	10.4
Total cholesterol, SI Units (SD)	4.5 (1.0)	4.5 (1.0)
High-density lipoprotein, SI Units (SD)	1.3 (0.4)	1.4 (0.4)
eGFR, ml/min/1.73m^2 (SD)	58.4 (18.3)	55.4 (18.6)
Albumin-to-creatinine ratio, mg/g (IQI)	7.1 (3.5, 18.5)	8.2 (3.8, 23.7)

*Number represents participants who did not undergo two-week continuous ECG monitoring and who were not missing covariates of interest listed in this table

Appendix C: Supplementary materials for Chapter 3

Figure C-1. Study flow diagram

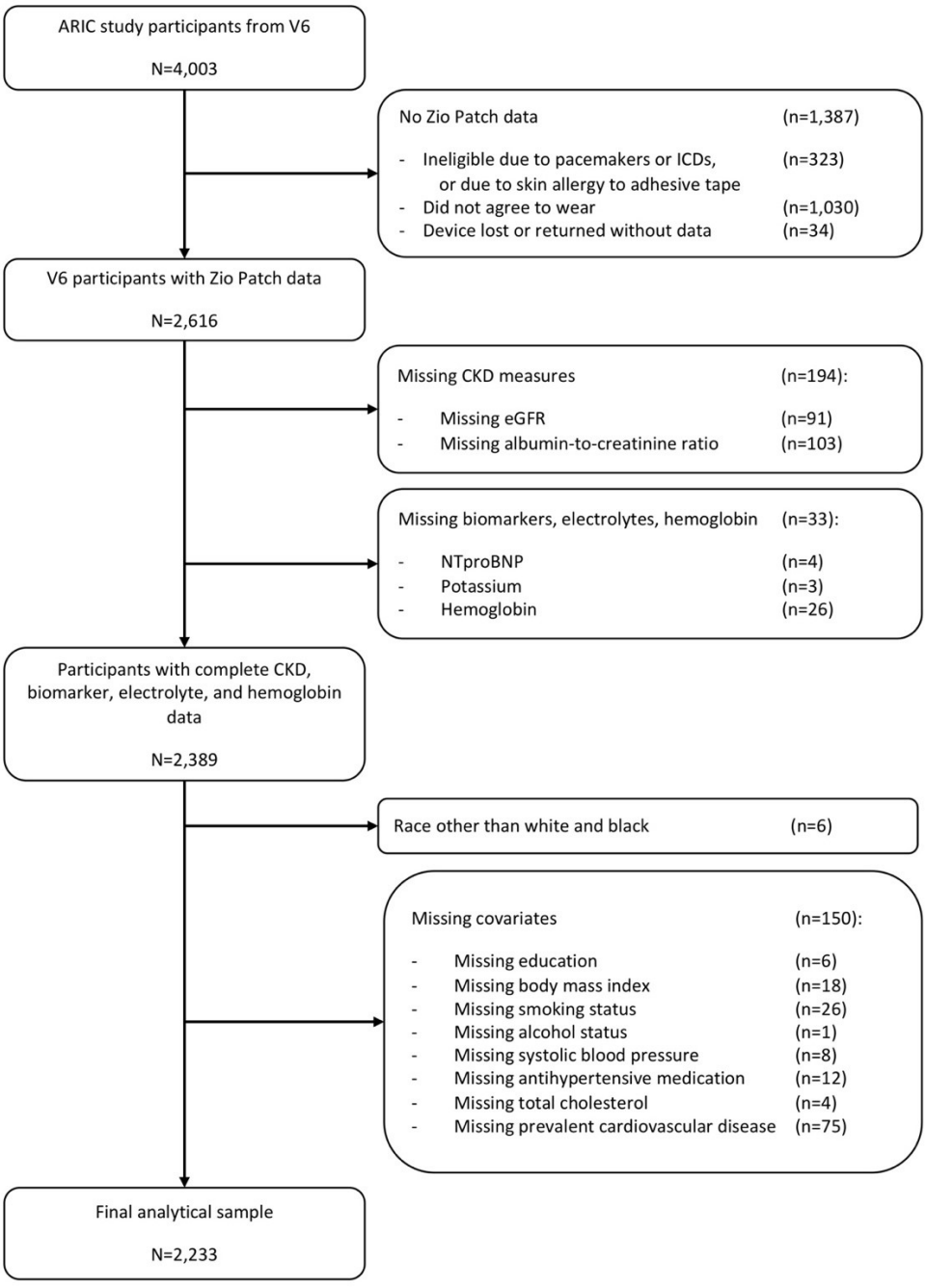


Table C-1. List of drugs commonly associated with QT-prolongation and torsades de pointes

Antiarrhythmic	Antimicrobial	Antidepressant	Antipsychotic	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Setraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

*Accessed from https://www.uspharmacist.com/article/drug-induced-qt-prolongation

Table C-2. Burden of major and minor arrhythmias by chronic kidney disease (CKD) status

Characteristics	Total n=2233	No CKD n=933	CKD n=1300
Major arrhythmias			
Atrial fibrillation			
Presence, %	7.4	5.0	9.2
Percent of time in arrhythmia (IQI)*, %	100 (6, 100)	11 (2, 100)	100 (5, 100)
Non-sustained ventricular tachycardia			
Presence, %	30.2	25.8	33.4
Frequency (number of episodes per day [IQI])*	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Long pause			
Presence, %	2.7	1.7	3.4
Frequency (number of episodes per day [IQI])*	0.2 (0.1, 1.3)	0.2 (0.1, 0.7)	0.2 (0.1, 1.8)
Atrioventricular block			
Presence, %	1.7	1.9	1.6
Frequency (number of episodes per day [IQI])*	0.2 (0.1, 0.6)	0.1 (0.1, 0.6)	0.3 (0.1, 0.7)
Minor arrhythmias			
Ventricular ectopy			
Presence, %	98.8	98.6	99.0
Frequency (number of episodes per day [IQI])*	68.7 (11.6, 420.9)	54.3 (7.9, 339.4)	78.2 (14.8, 488.6)
Supraventricular tachycardia§			
Presence, %	89.7	91.2	88.6
Frequency (number of episodes per day [IQI])*	0.9 (0.4, 2.2)	0.9 (0.4, 2.2)	0.8 (0.3, 2.2)
Supraventricular ectopy§			
Presence, %	99.9	99.8	99.9
Frequency (number of episodes per day [IQI])*	202.3 (63.5, 803.7)	170.8 (58.5, 722.8)	227.8 (67.3, 846.5)

*Characteristics are summarized only among participants with presence of the corresponding arrhythmia
§Among participants who do not have chronic atrial fibrillation

Table C-3. Number of non-sustained ventricular tachycardia episodes per day by quartiles of hs-cTnT in no-CKD and in CKD

	No CKD				CKD			
	hs-cTnT Q1	**hs-cTnT Q2**	**hs-cTnT Q3**	**hs-cTnT Q4**	**hs-cTnT Q1**	**hs-cTnT Q2**	**hs-cTnT Q3**	**hs-cTnT Q4**
Number of episodes/day, mean (SD)	0.224 (3.439)	0.036 (0.085)	0.079 (0.266)	0.085 (0.156)	0.034 (0.098)	0.043 (0.129)	0.108 (0.704)	0.270 (2.830)

hs-cTnT=high-sensitivity cardiac troponin T; CKD=chronic kidney disease; Q1=quartile 1; Q2=quartile 2; Q3=quartile 3; Q4=quartile 4; SD=standard deviation

Table C-4. Summary of associations of cardiac biomarkers, electrolytes, and hemoglobin with arrhythmias by chronic kidney disease status

	NTproBNP, per 2-fold higher		hs-cTnT, per 2-fold higher		Potassium <4.1 mmol/l, per 1 mmol/l lower		Potassium >4.1 mmol/l, per 1 mmol/l higher		Magnesium <2 mg/dl, per 0.5 mg/dl lower		Magnesium >2 mg/dl, per 0.5 mg/dl higher		Hemoglobin, per 1 g/dl lower	
	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD
Atrial fibrillation														
Presence	↑	↑	↑	↑	↑					↑				
% time	↑	↑	↑							↑				
Ventricular tachycardia														
Presence	↑	↑	↑	↑										
Frequency	↑	↑		↓			↓					↑		
Long pause														
Presence	↑	↑									↑			
Frequency	↑	↑		↑										
Atrioventricular block														
Presence														
Frequency		↑	↓					↑		↓		↓		
Ventricular ectopy														
Presence	↑													
Frequency	↑	↑				↑								
Supraventricular tachycardia														
Presence														
Frequency											↓			↓
Supraventricular ectopy														
Presence														
Frequency	↑	↑		↑							↓	↓		

↑ Indicates positive association after adjusting for potential confounders
↓ Indicates negative association after adjusting for potential confounders

Appendix D: Supplementary materials for Chapter 4

Figure D-1. Study flow diagram

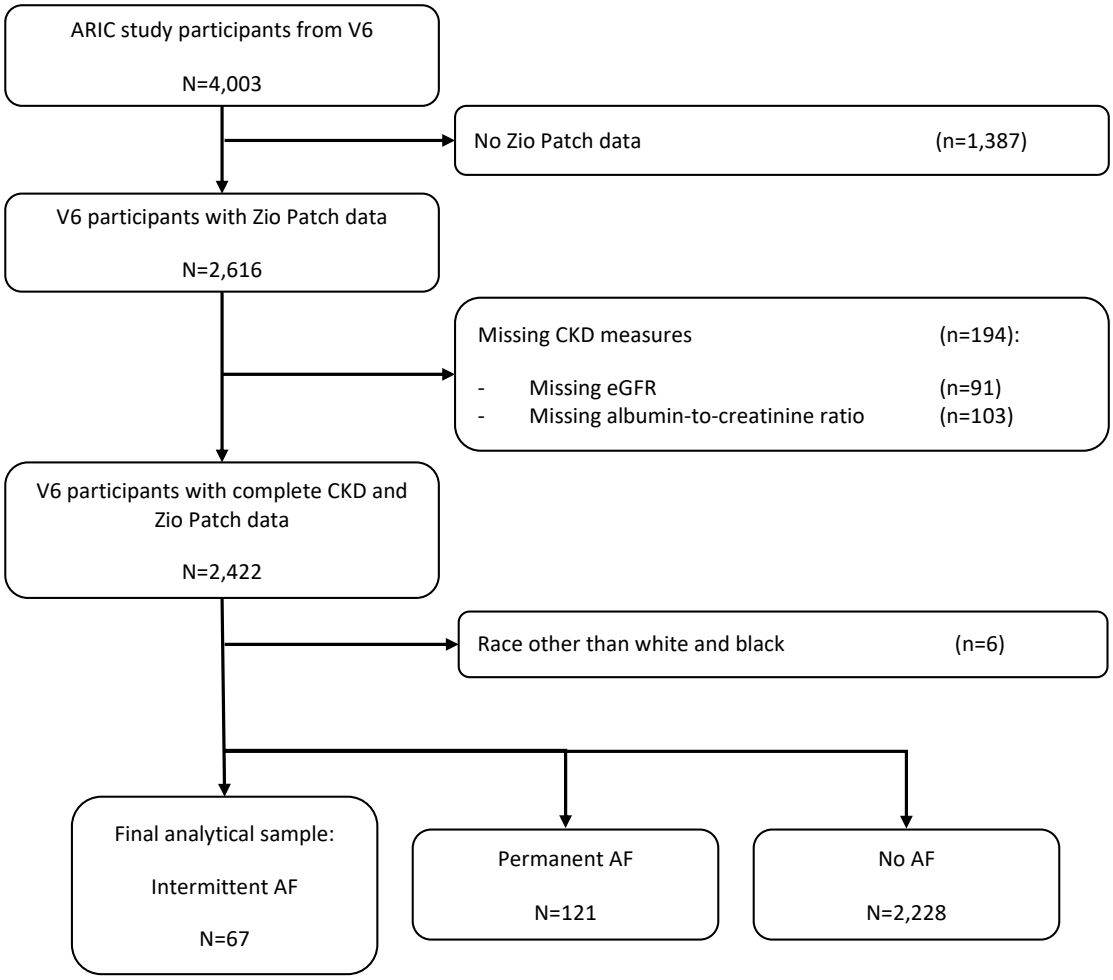
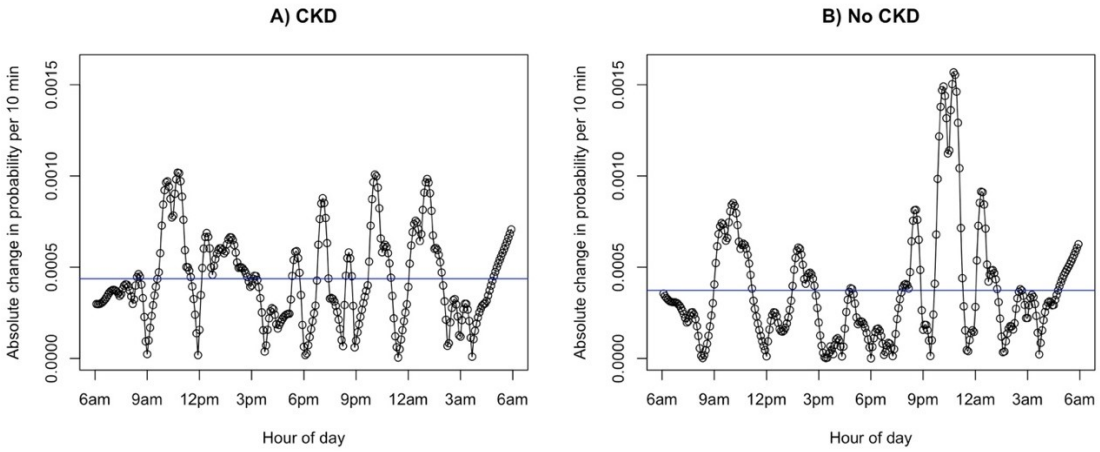


Table D-1. List of drugs commonly associated with QT-prolongation and torsades de pointes

Antiarrhythmic	Antimicrobial	Antidepressant	Antipsychotic	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Setraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

*Accessed from https://www.uspharmacist.com/article/drug-induced-qt-prolongation

Figure D-2. Absolute change in probabilities of atrial fibrillation over time by chronic kidney disease status



Blue line represents the mean absolute change in probability of atrial fibrillation per 10 min over 24 hours.

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Curriculum Vitae

Esther Kim

Educational Background

2016-Present **Johns Hopkins Bloomberg School of Public Health**
Baltimore, Maryland
Doctor of Philosophy (Ph.D.) in Epidemiology

2013-2015 **University of Toronto Dalla Lana School of Public Health**
Toronto, Ontario
Master of Public Health (M.P.H.) in Epidemiology

2009-2013 **University of Toronto**
Toronto, Ontario
Honours Bachelor of Science (H.B.Sc.) with High Distinction

Awards and Distinction

Sep 2019 **FastForward Innovation Award**
MedHacks at Johns Hopkins University
Baltimore, Maryland

Mar 2019 **Student Travel Support Fund**
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

Apr 2018 **Louis I. Dublin and Thomas D. Dublin Fund for the Advancement of Epidemiology and Biostatistics**
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

May 2017 **Moyses Szklo Teaching Fellowship**
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

Oct 2016 **ClearEdge's Best Data Driven Project Award**
HackUMBC at University of Maryland Baltimore County
Baltimore County, Maryland

Oct 2016	**Lyft's Best Use of Lyft API Award** HackUMBC at University of Maryland Baltimore County Baltimore County, Maryland
Jun 2016	**AstraZeneca Impact Challenge Grant** Heart and Stroke Richard Lewar Center Toronto, Ontario
Jun 2016	**New Seed Funding Award** Canadian Vascular Network Toronto, Ontario
2010-2013	**Dean's List Scholar** University of Toronto Toronto, Ontario
2012	**e-Health Apps Challenge Finalist Award** National e-Health Annual Conference Vancouver, British Columbia
2010-2012	**Trinity College In-Course Scholarship** University of Toronto Toronto, Ontario

Work Experience

Nov 2016- Present	**Research Assistant** Department of Epidemiology Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland
Jun 2019- Aug 2019	**Research Scientist Intern** Facebook Seattle, Washington
Nov 2018- Jan 2019	**Associate Intern** Sage Growth Partners Baltimore, Maryland
Nov 2016- Feb 2017	**Open Data Intern** Kaggle San Francisco, California

May 2016- **Biostatistician**
May 2017 Human Heredity and Health in Africa (H3Africa) Initiative
Toronto, Ontario

Jul 2015- **Clinical Research Project Assistant**
Jul 2016 The Hospital for Sick Children
Toronto, Ontario

Sep 2013- **Graduate Research Student**
Jun 2015 The Hospital for Sick Children
Toronto, Ontario

Sep 2013- **Junior Statistician**
May 2014 Toronto General Hospital
Toronto, Ontario

May 2012- **Clinical Research Student**
May 2013 Toronto General Research Institute
Toronto, Ontario

Teaching Experience

Oct 2019- **Teaching Assistant**
Dec 2019 Course: Intermediate Epidemiology (600.702.86)
Johns Hopkins Bloomberg School of Public Health

Mar 2019- **Teaching Assistant**
May 2019 Course: Statistical Concepts in Public Health I (600.709.86)
Johns Hopkins Bloomberg School of Public Health

Jul 2018- **Teaching Assistant**
Aug 2018 Course: Principles of Epidemiology (340.601)
Johns Hopkins Bloomberg School of Public Health

Nov 2017- **Teaching Assistant**
May 2018 Course: Epidemiologic Methods 2 (340.752)
Johns Hopkins Bloomberg School of Public Health

Course: Epidemiologic Methods 3 (340.753)
Johns Hopkins Bloomberg School of Public Health

Sep 2017- Oct 2017 **Lead Teaching Assistant**
Course: Epidemiologic Methods 1 (340.751)
Johns Hopkins Bloomberg School of Public Health

Jun 2017 **Teaching Assistant**
Course: Application and Methods of Cohort Studies (340.706)
Johns Hopkins Bloomberg School of Public Health

Jun 2016 **Teaching Assistant**
Course: Application and Methods of Cohort Studies (340.706)
Johns Hopkins Bloomberg School of Public Health

Peer-Reviewed Publications

Kim ED, Ballew SH, Tanaka H, Heiss G, Coresh J, Matsushita K. Short-term prognostic impact of arterial stiffness in community-dwelling older adults: The Atherosclerosis Risk in Communities (ARIC) Study. *Hypertension*. 2019

Rogovoy N, Howell S, Lee T, Hamilton C, Perez-Alday E, Kabir M, Zhang Y, **Kim ED**, Fitzpatrick J, Monroy-Trujillo J, Estrella M, Sozio S, Jaar BG, Parekh R, Tereshchenko L. Hemodialysis Procedure Associated Autonomic Imbalance and Cardiac Arrhythmias: Insights from Continuous 14-day ECG Monitoring. *Journal of American Heart Association*. 2019.

Kim ED, Watt J, Tereshchenko LG, Jaar BG, Sozio SM, Kao WH, Estrella MM, Parekh RS. Associations of serum and dialysate electrolytes with arrhythmic risk in incident hemodialysis: The Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study. *BMC Nephrology*. 2019.

Liu S, **Kim ED***, Wu A, Meyer M, Cheng S, Hoogeveen R, Ballantyne C, Tanaka H, Heiss G, Selvin E, Matsushita K. Central and peripheral pulse wave velocity and subclinical myocardial stress and damage in older adults. *PLOS ONE.* 2019.

Matsushita K, Ding N, **Kim ED,** Budoff M, Chirinos JA, Hamburg NM, Kario K, Miyoshi T, Tanaka H, Townsend R. Cardio-ankle vascular index and cardiovascular disease: systematic review and meta-analysis of prospective and cross-sectional studies. *The Journal of Clinical Hypertension*. 2018.

Kim ED, Tanaka H, Ballew SH, Sang Y, Heiss G, Coresh J, Matsushita K. Associations between kidney disease measures and regional pulse wave velocity in a large community-based cohort: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Kidney Diseases*. 2018.

Kerns E, **Kim ED**, Meoni L, Jaar BG, Sozio SM, Estrella MM, Parekh RS, Bourjelly G. Obstructive Sleep Apnea in Hemodialysis Patients is Associated with a Higher Risk for Sudden Cardiac Death. 2018. *American Journal of Nephrology*.

Kim ED, Meoni LA, Jaar BG, Shafi T, Kao WH, Estrella MM, Parekh RS, Sozio SM. Association of Arterial Stiffness and Central Pressure with Cognitive Function in Incident Hemodialysis. *Kidney International Reports*. 2017.

Chanchlani R, Kim SJ, **Kim ED,** Banh T, Borges K, Vasilevska-Ristovska J, Li Y, Ng V, Dipchand A, Solomon M, Herbert D, Parekh RS. Incidence of hyperglycemia and diabetes and association with electrolyte abnormalities in pediatric solid organ transplant recipients. 2017. *Nephrology Dialysis Transplantation*. doi.org/10.1093/ndt/gfx205

Cattran DC, **Kim ED**, Reich H, Hladunewich M, Kim SJ. Membranous Nephropathy: Quantifying the Impact of Remission Duration on Outcome. *Journal of the American Society of Nephrology*. 2016. doi: 10.1681/ASN.2015111262

Tereshchenko L, **Kim ED**, Oehler A, Meni LA, Ghafoori E, Rami T, Maly M, Kabir M, Hawkins L, Tomaselli G, Lima JA, Jaar BG, Sozio SM, Estrella MM, Kao WH, Parekh RS. Electrophysiological Substrate and Risk of Mortality in Incident Hemodialysis: the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study. *Journal of the American Society of Nephrology*. 2016. 27(11): 3413-3420.

Kim ED, Parekh RS. Calcium and Sudden Cardiac Death in End-Stage Renal Disease. *Seminars in Dialysis.* 2015. 28(6): 625-35.

Kim ED, Sozio SM, Estrella MM, Jaar BG, Shafi T, Meoni LA, Kao WH, Lima JA, Parekh RS. Cross-sectional association of volume, blood pressures, and aortic stiffness with left ventricular mass in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. 2015. *BMC Nephrology.* 16:131.

Kim ED, Famure O, Li Y, Kim SJ. Uric Acid and the Risk of Graft Failure in Kidney Transplant Recipients: A Re-Assessment. *American Journal of Transplantation.* 2015. 15(2): 482-8.

* Indicates co-first authorship

Abstracts

Kim ED, Coresh J, Matsushita K, Chen LY, Zipunnikov V. Diurnal patterns of intermittent atrial fibrillation by chronic kidney disease status: The Atherosclerosis Risk in Communities (ARIC) Study. *American Heart Association Epi-Lifestyle Scientific Session.* 2020. **Poster presentation.**

Kim ED, Ding N, Ishigami J, Hishida M, Ning X, Feng Y, Coresh J, Chen LY, Matsushita K. Chronic Kidney Disease and Cardiac Arrhythmias: A Systematic Review and Meta-Analysis. *American Heart Association Epi-Lifestyle Scientific Session.* 2020. **Poster presentation.**

Kim ED, Hoogeven R, Selvin L, Ballantyne C, Soliman EZ, Coresh J, Matsushita K, Chen LY. Cardiac Biomarkers, Electrolytes, and Anemia with Arrhythmias over Two Weeks in Chronic Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study. *American Heart Association Epi-Lifestyle Scientific Session.* 2019. **Poster presentation.**

Kim ED, Soliman EZ, Coresh J, Matsushita K, Chen LY. Prevalence of arrhythmias based on two-week continuous monitoring across severity of chronic kidney disease: The Atherosclerosis Risk in Communities (ARIC) Study. *American Heart Association Scientific Session.* 2018. **Poster presentation.**

Kim ED, Ding N, Ballew SH, Tanaka H, Heiss G, Coresh J, Matsushita K. Short-term prognostic impact of arterial stiffness in community-dwelling older adults: The Atherosclerosis Risk in Communities (ARIC) Study. *American Heart Association Scientific Session.* 2018. **Poster presentation.**

Liu S, **Kim ED**, Wu A, Meyer M, Cheng S, Hoogeveen R, Ballantyne C, Tanaka H, Heiss G, Selvin E, Matsushita K. Central and peripheral pulse wave velocity and subclinical myocardial stress and damage in older adults: the Atherosclerosis Risk in Communities (ARIC) study. *American Heart Association Epi-Lifestyle Scientific Session.* 2018. **Poster presentation.**

Kerns E, **Kim ED**, Meoni L, Jaar BG, Sozio SM, Estrella MM, Parekh RS, Bourjelly G. Obstructive Sleep Apnea and Risk of Mortality in Incident Hemodialysis: the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study. *American Society of Nephrology.* 2016. **Oral presentation.**

Kim ED, Meoni L, Jaar BG, Sozio SM, Estrella MM, Parekh RS. Association of Vitamin K and Subclinical Cardiovascular Disease in Incident Hemodialysis: the

Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study. *American Society of Nephrology.* 2016. **Poster presentation.**

Kabir M, Sedaghat G, Meoni L, **Kim ED**, Rami T, Maly M, Lima J, Jaar B, Sozio S, Estrella M, Kao L, Parekh R, Tereshchenko L. Very-Low Frequency Heart Rate Variability is Depressed During Hemodialysis Session. *International Society for Computerized Electrocardiography Meeting.* 2016. **Poster presentation.**

Tereshchenko L, Oehler A, Meni LA, Ghafoori E, **Kim ED,** Rami T, Maly M, Kabir M, Hawkins L, Lima JA, Jaar BG, Sozio SM, Estrella MM, Kao WH, Parekh RS. Electrophysiological Substrate and Risk of Mortality in Incident Hemodialysis: the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study. *American Heart Association Scientific Sessions.* 2015. **Poster presentation.**

Kim ED, Meoni LA, Jaar BG, Shafi T, Kao WH, Estrella MM, Parekh RS, Sozio SM. Association of Arterial Stiffness with Cognitive Impairment in Incident Hemodialysis. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Watt J, **Kim ED,** Tereshchenko L, Sozio SM, Jaar BG, Meoni LA, Estrella MM, Parekh RS. Association of Serum and Dialysate Electrolytes with Arrhythmic Risk in Incident Hemodialysis. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Kim ED, Sozio SM, Jaar BG, Meoni LA, Estrella MM, Parekh RS. Association of Circulating Biomarkers with Vascular Stiffness and Coronary Artery Calcium in Incident Hemodialysis. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Koubar S, **Kim ED,** Segev DL, Sozio SM, Tereshchenko L, Meoni LA, Parekh RS, Estrella MM. Association of Klotho and FGF23 with Frailty in Patients Initiating Hemodialysis. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Johns T, **Kim ED,** Kimberly Novick T, Meoni LA, Sozio SM, Jaar BG, Tereshchenko L, Parekh RS, Estrella MM. Differential Association of Fibroblast Growth Factor-23 and Soluble Klotho with Left Ventricular Hypertrophy. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Toth-Manikowski SM, **Kim ED,** Meoni LA, Jaar BG, Shafi T, Estrella MM, Parekh RS, Sozio SM. Predictors of Arterial Stiffness in Incident Hemodialysis Patients. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Menez S. Estrella MM, **Kim ED,** Meoni LA, Matsushita K, Garimella P, Sozio SM, Parekh RS, Jaar BG. Association of Vascular Calcification Biomarkers with Peripheral Arterial Disease in Hemodialysis Patients. *American Society of Nephrology Kidney Week.* 2015. **Poster presentation.**

Garimella PS, Kwak L, Matsushita K, **Kim ED,** Estrella MM, Sozio SM, Meoni LA, Parekh RS, Jaar BG. Ankle Brachial Index and Exertional Leg Pain Among Hemodialysis Patients without a Clinical Diagnosis of Peripheral Arterial Disease. *American Society of Nephrology Kidney Week.* 2015.

Cattran D, **Kim ED,** Kim SJ, Reich H, Hladunewich M. Duration of Remission and Outcome in Membranous Nephropathy: A Landmark Analysis. *Canadian Society of Nephrology Meeting.* 2015. **Poster presentation.**

Kim ED, Meoni L, Jaar B, Shafi T, Estrella M, Parekh R, Sozio S. Is arterial stiffness associated with cognitive impairment in hemodialysis patients? *Canadian Society of Epidemiology and Biostatistics*. 2015. **Oral presentation**.

Kim ED, Kim SJ, Reich H, Hladunewich M, Cattran D. Landmark Association of the Duration of Remission and Outcome in Membranous Nephropathy. *Canadian Society of Epidemiology and Biostatistics.* 2015. **Oral presentation.**

Kim ED, Sozio S, Estrella M, Jaar B, Shafi T, Meoni L, Kao L, Parekh S. Is arterial stiffness, blood pressure, or volume status associated with left ventricular mass in hemodialysis? *The Hospital for Sick Children Department of Pediatrics Research Day*. 2015**. Poster presentation**.

Cattran D, **Kim ED,** Hladunewich M, Reich H, Kim J. Duration of remission in membranous nephropathy: Can we quantitate its value? *World Congress of Nephrology*. 2015. **Oral presentation**.

Chanchlani R, **Kim ED**, Banh T, Borges K, Vasilevska-Ristovska J, Li Y, Ng V, Dipchand A, Solomn M, Herbert D, Kim J, Parekh S. Are hypomagnesemia and hypokalemia risk factors for hyperglycemia and new onset diabetes after pediatric solid organ transplantation? *International Pediatric Transplant Association*. 2015. **Oral presentation**.

Kim ED, Sozio S, Estrella M, Jaar B, Shafi T, Meoni L, Kao L, Parekh S. Association of afterload and preload with left ventricular mass in incident hemodialysis patients: Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. *American Society of Nephrology Kidney Week*. 2014. **Poster presentation**.

Kim ED, Sozio S, Estrella M, Jaar B, Shafi T, Meoni L, Kao L, Parekh S. Is arterial stiffness, blood pressure, or volume status associated with left ventricular mass in persons on dialysis? *Canadian Society of Epidemiology and Biostatistics*. 2014. **Oral presentation**.

Kim ED, Famure O, Huang J, Zyla R, Kim SJ. Early hospital re-admission and outcomes after kidney transplantation. *American Society of Nephrology Kidney Week*. 2014. **Poster presentation**.

Famure O, **Kim ED,** Zyla R, Huang J, Kim SJ. Early Hospital Readmission after Kidney Transplantation: Incidence, Causes, and Risk Factors**.** *American Society of Nephrology Kidney Week***.** 2014. **Poster presentation.**

Kim ED, Famure O, Li Y, Kim J. Is uric acid an independent risk factor for graft failure in kidney transplant recipients? *American Transplant Congress*. 2013. **Poster presentation**.

Peer Review Experience

July 2018 PLOS One

Academic and Community Activities

Sep 2016-Present **Trainee Coordinator**
Welch Center for Prevention, Epidemiology and Clinical Research
Baltimore, Maryland

2017-2019 **Co-Chair, Alumni Relations**
Epidemiology Student Organization (ESO)
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

2017-2019 **Student Mentor**
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health

Baltimore, Maryland

2016-2017 **Community Consultant**
National Alliance on Mental Illness (NAMI) Baltimore
Baltimore, Maryland